The Healing of Nerves

Charles Ballance and Purves Stewart

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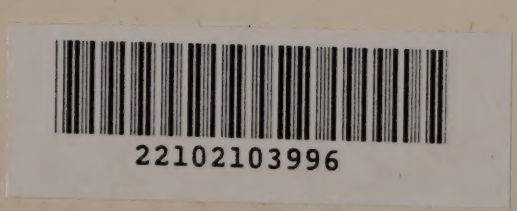

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THE HEALING OF NERVES

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BY

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αἰεὶ τὰ φεύγοντα δίζηνται κιχεῖν.

Bacchylides, *Ode* 1.

Labor ipse voluptas.

Manilius, *Astron.* iv.

All things that are,
Are with more spirit chased than enjoy'd.

Merchant of Venice, Act II. Scene 6.

To travel hopefully is a better thing than to arrive, and the true success is to labour.

Robert Louis Stevenson, *El Dorado.*

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A. S.
M.C.M.I.

PREFACE

The exact process whereby peripheral nerves, after they have been divided, become reunited, has been a subject of considerable controversy. The present research was undertaken with the object of solving some of the problems so raised, both with regard to degeneration and to regeneration.

Most of the work was already completed by the end of 1899, but the absence of one of us at the South African war for over a year has delayed its publication until the present date.

The experimental part of the work was performed at the Brown Institution, Vauxhall. The histological portion of the research was undertaken partly at Professor Weigert's laboratory in the Senkenbergisches Institut, Frankfort A/M, and partly at the laboratories of the Colleges of Physicians and Surgeons in London.

The employment of the Golgi method, which confirms in so striking a manner the results obtained by the other stains, was suggested to us by Prof. D. J. Cunningham.

We have also to express our indebtedness to Dr. David Orr, pathologist to the County Asylum, Prestwich, for his kindness in cutting a number of sections prepared by the Golgi method, and to Dr. James Collier for his assistance on several occasions.

The original drawings for the illustrations were made for us by Mr. M. H. Lapidge, to whose skill and painstaking accuracy we are much indebted. In those drawings whose direction is vertical the upper end in each case represents the proximal end of the section, the lower end being the distal.

CHARLES A. BALLANCE.
PURVES STEWART.

NOTE

I HAD long wished to investigate the vexed question of the healing of nerves. The many calls on my time and my lack of experience of modern microscopical methods made this wish difficult of attainment. Dr. Purves Stewart has filled the gap, and the large number of preparations on which this paper is based are the result of his knowledge and his energy. The merit then, if any, of this volume belongs to him.

CHARLES A. BALLANCE.

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CHAPTER I

INTRODUCTORY

Objects of the Research

The chief problems with which this work is concerned are as follows :—

1. The process of degeneration in a peripheral nerve after injury ; (*a*) without, and (*b*) with, immediate suturing of the proximal to the distal segment.
2. The process of regeneration in a nerve-trunk which has been divided and subsequently reunited by suture.
3. The process of regeneration, if any, in the distal segment of a nerve-trunk which has been divided, but in which the proximal and distal segments have not been brought into apposition.
4. The changes which occur in nerve-grafts ; *i.e.* where a portion of nerve is interposed between the proximal and distal segments of a divided nerve, to replace a portion which had previously been removed.

Methods employed

The animals selected for systematic observation were monkeys,

dogs, and cats. A number of specimens were also obtained during operations on the human subject for the relief of injuries to various nerves. The specimens, after fixing in Müller's fluid, or in solution of formalin, were stained by one of the following four methods :—

1. Weigert's method for the selective staining of the medullary sheaths.

2. Cox's modification of the Golgi method for the impregnation of the axis-cylinders.

3. Stroebe's method for the staining of the axis-cylinders.

4. Van Gieson's method for the staining of the cellular and protoplasmic structures.

Plan of Experiments

In every case the animal was fully anæsthetised by chloroform or ether.

1. Division of a large nerve-trunk and immediate suture.

In these experiments the method employed was as follows :—

The nerve was exposed and divided half-way across. A strand of horsehair was now inserted into the notch. The horsehair loop served to steady the nerve during the application of sutures. The edges of the notch were then brought together by two or three fine silk sutures threaded on the finest round intestinal curved needles. By this means the strand of horsehair was buried at the bottom of the notch at which it had entered. The horsehair thread was then cut out on the

opposite side of the nerve from that on which it had entered, thereby completing the division of the nerve-trunk. The wound of exit was finally sutured in a similar manner.

2. Division of a large nerve-trunk, the cut ends being left unsutured.
3. Excision of a portion of a nerve-trunk, and transplantation of a portion of nerve sufficient to fill the gap, after varying periods of time.

The graft in such cases was taken sometimes from the same animal and sometimes from another animal. In the cases of "immediate transplantation" the process adopted was simply that of total division and immediate suture at two levels, the intervening portion representing the graft. In cases where a period of time was allowed to elapse after the excision of a portion of nerve, the graft was procured from another animal.

CHAPTER II

THE MYELIN SHEATHS

In the following series of observations the nerves were stained by Weigert's selective stain for the medullary sheaths. The results, in our experience, are more constant and more reliable than those obtained by the use of other staining methods.

Observation 1

Cat. Sciatic nerve. Divided. Ends not sutured.
Specimen obtained 12 *hours* later.

Histological appearances

(*a*) In the proximal end.—Some of the medullary sheaths near the site of division are broken up into oblong, coarsely granular masses, somewhat larger in diameter than the healthy medullary sheaths.

These granular masses are in many places at the distal end of the fibre; in some, however, a considerable length of unchanged sheath is present below such a mass.

The medullary sheaths at the free end are somewhat spread out from one another, and there is extravasation of

blood-corpuscles between them for some distance up the nerve.

A cap of perineurium with fat cells in it covers the end of the nerve.

(*b*) In the distal end.—No homogeneous coarsely granular masses are present like those in the proximal end.

The nerve has retracted considerably farther than in the proximal end, and its stump is covered by a much larger cap of perineurium with fat cells.

There is extravasation of blood between the medullary sheaths close to the line of division.

Observation 2

Cat. Sciatic nerve. Divided and immediately sutured.
12 *hours.*

The sections show—Normal medullary sheaths above and below the wound. Extravasation of blood-corpuscles in the vicinity of the lesion, both between the nerve-fibres and into the perineurium. The appearances are identical with those at the proximal end of the nerve in Observation 1.

Observation 3

Cat. Sciatic nerve. Divided, not sutured.
24 *hours.*

(*a*) In the proximal end.—The fibres at the free end are

spread out in a mushroom-like fashion (see Plate 1, fig. 1). The medullary sheaths stain normally, but near the free end of the divided fibres numerous sheaths are broken up into short segments, separated by imbricating or transverse divisions.

(*b*) In the distal end.—The medullary sheaths show breaking up into short segments about $\frac{1}{6}$ to $\frac{1}{8}$ of the length of the normal internodes. These short segments are apparently broken off from each other by imbricating cracks. They still stain quite normally.

Observation 4

Cat. Sciatic nerve. Divided and immediately sutured.
2 *days.*

The medullary sheaths at the level of the sutures have become broken up into coarsely granular débris, forming irregular lines of ovoid globules. In the immediate vicinity of the line of union the medullary sheaths, both of the proximal and distal ends, show pigmentation due to blood-extravasation, but at some distance below this level they do not differ in appearance from those of the normal fibres of the proximal end.

Observation 5

Cat. Sciatic nerve. Divided and not sutured.
2 *days*.

Proximal End

Beyond extravasation of blood between the nerve-fibres and the traumatic changes already described as occurring in the vicinity of the injury, no other change is observed.

Distal End

The fibres are found infiltrated with blood for some little distance down from the point of section.

Observation 6

Cat. Sciatic nerve. Divided and immediately sutured.
3 *days*.

The appearances do not materially differ from those seen in Observation 5 (after 2 days).

Observation 7

Cat. Sciatic nerve. Divided and not sutured.
3 *days*.

The sections show the following changes :—

(*a*) In the proximal end.—Layer of laminated blood-clot at the end of the nerve, close against the nerve-fibres.

The medullary sheaths are broken up into fragments near the cut end.

(*b*) In the distal end.—The medullary sheaths are somewhat less regular in outline than normal and of not quite uniform diameter, but, except close to the point of division of the nerve, there is no actual segmentation of the myelin sheaths.

Observation 8

Cat. Sciatic nerve. Divided and immediately sutured.
4 *days*.

The medullary sheaths have taken the stain in a distinctly less uniform manner on the distal than on the proximal side of the line of reunion.

With a high power peripheral fragmentation of the medullary sheath is seen commencing, in places, along the entire length of the distal fibres.

The myelin sheaths in the distal segment appear slightly more broken up in those portions of their course which lie nearest to the seat of injury than in portions farther off; but the general changes in the sheaths seem to have occurred simultaneously in their whole length and have not spread peripherally from the seat of the injury.

Observation 9

Cat. Sciatic nerve. Divided and not sutured.
4 *days*.
Distal end only examined.

There is slight peripheral fragmentation beginning here and there throughout the entire course of the myelin sheaths.

Observation 10

Cat. Sciatic nerve. Divided and sutured immediately.
5 *days*.

Fragmentation of the whole peripheral end is now uniformly established. Individual fragments of medullary sheaths are still arranged in longitudinal series and stain deeply with hæmatoxylin.

The finest myelin sheaths seem to be relatively less affected.

In the proximal end, similar fragmentation occurs in the vicinity of the wound only.

Observation 11

Cat. Sciatic nerve. Divided and not sutured.
5 *days*.

(*a*) In the proximal end.—Nothing of importance is seen save traumatic changes already described.

(*b*) In the distal end. — The medullary sheaths are markedly broken up into fragments in their entire length.

The finest sheaths are relatively less affected by this process (see Plate 1, fig. 2). They survive better than the adult sheaths, and are more readily seen than in a normal nerve in which they are outnumbered and to some extent obscured by their larger companions.

Observation 12

Cat. Sciatic nerve. Divided and immediately sutured. 6 *days*.

The appearances in the *distal* end are similar to those observed in Observation 11 (5 days) but more advanced. A fine surviving sheath is often found lying in close approximation to a broken-up large sheath, and apparently within the same neurilemma. The same appearances also occur for a short distance on the *proximal* side of the line of suture, where the fragmentation affects the larger sheaths to a greater extent than the finer ones.

Observation 13

Cat. Sciatic nerve. Divided and immediately sutured. 1 *week*.

There is marked fragmentation of the sheaths in the *distal*

segment. There is no longer any obvious survival of the fine sheaths such as was noted in Observations 10, 11, and 12 (5th and 6th days).

The myelin sheaths do not stain so deeply in the distal as in the proximal segment.

Observation 14

Cat. Sciatic nerve. Divided and not sutured.
1 *week.*

(*a*) In the proximal end.—Except for slight fragmentation of the myelin close to the plane of injury, the medullary sheaths appear normal.

(*b*) In the distal end.—The medullary sheaths are completely broken up into longitudinal rows of globules, staining irregularly; the central part of the myelin seems to have lost its staining capacity earlier than the peripheral part. The fine sheaths have shared in this fragmentation.

Observation 15

Monkey. Musculo-spiral. Divided and not sutured.
1 *week.*

The appearances resemble those found in Observation 11 (5th day in cat) and the fine medullary sheaths still show more power of resistance than the larger ones. The process of degeneration is thus somewhat slower in the monkey than in the cat.

Observation 16

Cat. Sciatic nerve. Divided and sutured immediately. *2 weeks.*

(*a*) Distal segment.—The medullary sheaths are reduced to a mass of longitudinally-arranged oblong or globular bodies, granular in appearance, with here and there a large deeply-staining ovoid nucleus situated either amongst the granular material or more usually to one side of it. The changes are equally intense in the entire length of the distal portion.

(*b*) The proximal segment of the nerve shows the old sheaths swollen and broken up into globular or ovoid masses at their free ends. At the lower end of the proximal segment new myelin sheaths are now evident, growing downwards within the canals formed by old neurilemma sheaths. When only one young myelin sheath occupies an old neurilemma, it does not course down its centre but lies close to the neurilemma. Often a whole leash of new myelin sheaths is seen within a single old neurilemma.

Here and there, below the free ends of the young sheaths, shorter segments of young sheaths are present, which have not yet joined on to the central sheaths. These isolated lines run longitudinally and are situated just beneath a neurilemma which, higher up, corresponds

to a normal adult fibre. The young sheaths can be traced down to the proximal side of the connective-tissue mass which intervenes between the proximal and distal ends of the nerve but not through it (see Plate 1, fig. 3).

Observation 17

Cat. Sciatic nerve. Divided, ends not sutured.
2 weeks.

Distal segment.—The myelin sheaths are reduced to a number of longitudinally-arranged elongated or circular areas, some of which take up the stain while others do not stain at all. The unstained areas are made up of nucleated cells of varying size, closely huddled together within longitudinal barriers. Nowhere can any new sheaths be seen in process of formation.

Observation 18

Dog. Sciatic nerve. Divided, not sutured.
3 weeks.

In the *proximal* segment.—Formation of young myelin sheaths is going on at the free end and also throughout the crumpled neurilemma sheaths of the stump.

Here and there new sheaths are observed twisting in a spiral fashion within an old neurilemma (see Plate 1, fig. 4).

Observation 19

Cat. Sciatic nerve. Divided and not sutured.
3 *weeks*.

On the *distal* side of the wound there is marked degeneration with no sign of formation of new myelin sheaths.

On the *proximal* side of the wound the free end of the nerve shows new sheaths in process of development. These do not grow out continuously from the proximal end, but are arranged longitudinally in little islets. Apparently many islets develop within a single neurilemma. The process of development is as follows :—Two or more longitudinal streaks appear, roughly parallel to each other, at quite a distance from the nearest young sheaths on the proximal side. The young sheaths grow longitudinally to meet other similar sheaths until a continuous chain is formed.

These young sheaths can be traced close down to the scar-tissue which unites the two ends of the divided nerve but not into the scar-tissue itself.

In sections at varying distances below the site of division there is well-marked fragmentation of medullary sheaths. No new myelin sheaths are present at these levels.

FIG. 1.

Cat. Sciatic. Divided and not sutured. 24 hours.
To show "*primitive end bulb*" of proximal segment (× 50).
A. Trunk of nerve.
B. "Mushroom."

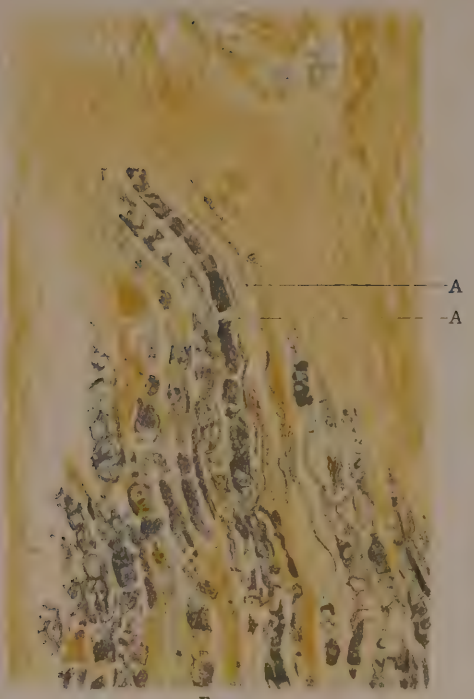
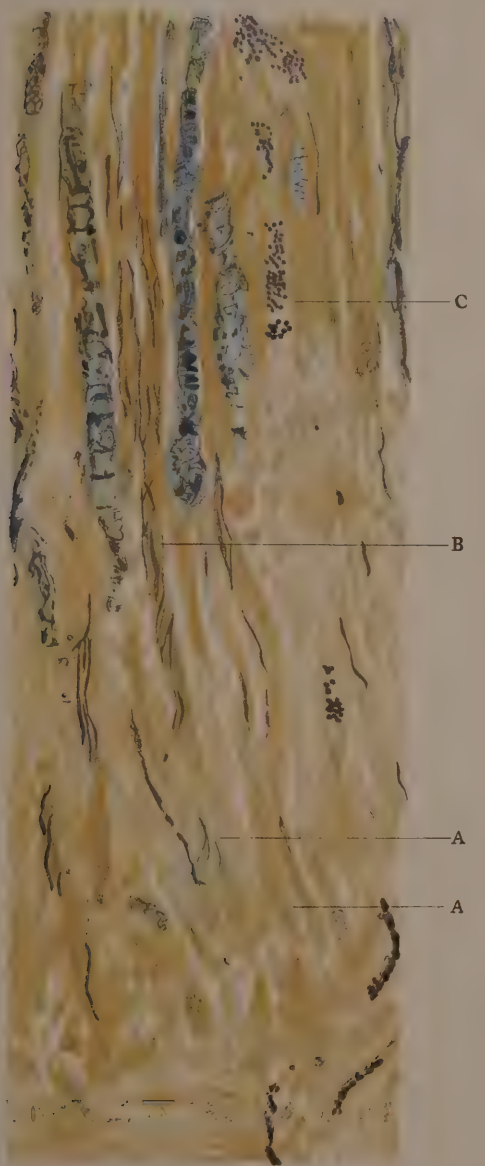


FIG. 2.

Cat. Sciatic. Divided and not sutured. 5 days.
To show degeneration of medullary sheaths in distal segment (× 200).
The plane of division is at the upper part of the drawing.
A.A. Fine sheaths as yet undegenerated.



M.H Lapidge.

FIG. 3.

Cat. Sciatic. Immediate reunion. 2 weeks.
To show early formation of new sheaths in lower end of central segment (× 200). Scar-tissue at lowest part of drawing.
A. Islands of new sheaths.
B. Continuous tubular plexus formed by adjacent islands.
C. Blood-vessel.

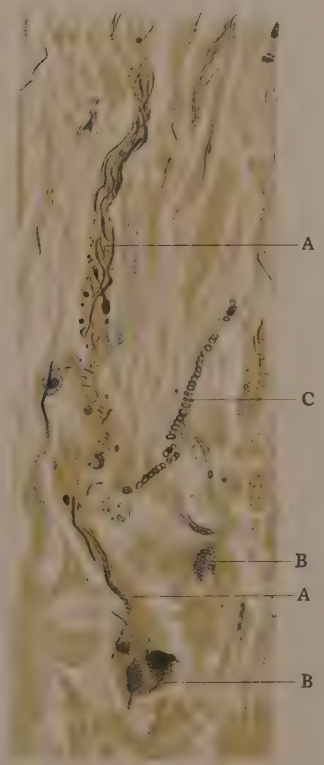


FIG. 4.

Dog. Sciatic. Divided and not sutured. 3 weeks.
To show well-marked spiral tubular plexus in lower end of proximal segment (× 200).
A.A. Spiral plexus of new sheaths.
B. Degenerated remains of old sheaths.
C. Capillary.

Observation 20

Cat. Sciatic nerve. Divided and immediately sutured.
3 *weeks.*

Young fibres are developing in the *proximal* segment, close down to the scar, amongst the degenerated and fragmented masses of old medullary sheaths.

The process in the proximal segment is exactly the same as in a nerve not sutured (Observation 18).

No young fibres can be detected amongst the broken up medullary sheaths of the *distal* segment.

Observation 21

Cat. Sciatic nerve. Divided and immediately sutured.
4 *weeks.*

Proximal segment.—The young myelin sheaths have increased to an enormous extent and form a host of parallel leashes, each separate leash of young sheaths having originated within a single old neurilemma (compare Plate 1, fig. 4, and Observation 18).

As we approach the scar-tissue from above, the new myelin sheaths become much less abundant and fade away into isolated lines of short length, arranged longitudinally one above another.

In the intervening *scar-tissue* the young myelin sheaths again become somewhat more abundant. Here they form an irregular network of crossing and interlacing lines, not arranged in a definite longitudinal fashion but interlacing amongst the globules of the profoundly degenerated medullary sheaths.

In the *distal* segment of the nerve, below the scar-tissue, the new sheaths are many times more numerous than in the scar-tissue itself. They are arranged in parallel rows and bundles, many of the bundles of new myelin sheaths embracing the globular degenerated remains of the old (*i.e.* they are within the neurilemma).

The new myelin sheaths show in places fusiform or moniliform thickenings, and thread their way between the masses of old degenerated myelin. They are equally abundant all the way down the nerve, and certainly more abundant than in the intervening scar-tissue. The moniliform thickenings on the myelin sheaths are due to the presence of long spindle-shaped cells lying along the course of the new sheaths.

Observation 22

Dog. Sciatic nerve. Divided and not sutured.
4 *weeks*.

(*a*) In the proximal end.—Young myelin sheaths can be traced into the connective tissue capping the stump of the nerve.

(*b*) In the distal end.—Here and there amongst the broken-up masses of myelin very fine black threads can be seen developing along one side of a longitudinally-lying elongated nucleus (see Plate 2, fig. 5).

Observation 23

Cat. Sciatic nerve. Divided and immediately sutured at two places half an inch apart. (This is equivalent to transplantation or grafting of the intervening half-inch of nerve).

4 *weeks*.

In the *proximal* segment new myelin sheaths are developing as in specimen (Observation 21) four weeks after suture of divided nerve.

In the *distal* segment, below the graft, very fine black lines are sparsely distributed as in the distal portion of a non-united nerve of similar date (Observation 22).

In the *graft* itself no new myelin sheaths can be detected.

Observation 24

Monkey. Musculo-spiral. Divided and not sutured. Fibrous junction afterwards took place.

30 *days*.

In the *proximal* segment young myelin sheaths are growing out, as in specimens already described.

In the *distal* segment some new myelin sheaths are seen in their earliest stage as fine hair-like lines, each in apposition to a

spindle-shaped cell. Under a high power (× 1000) these lines are resolvable into small discrete bodies in the protoplasm of the cell. They do not extend into the area of fibrous junction (see Plate 2, figs. 6 and 7).

Observation 25

Cat. Sciatic nerve. Divided and not sutured. Fibrous junction of the two ends afterwards took place.

5 *weeks.*

The *proximal* segment is shooting out numerous new myelin sheaths. These are just commencing to form the permanent "end bulb" by apparently curving back again on themselves like the water at the apex of a fountain.

On examination with a high power each of the young myelin sheaths is seen in close apposition to an apparently degenerated old fibre, and arises within the neurilemma as already described (Observation 21).

In the *distal* segment there appear at first sight no new myelin sheaths, but on careful examination a few faint black wavy lines are observed, longitudinal in direction, and in apposition to the faintly stained cells of the neurilemma (see Plate 3, fig. 10).

Half an inch below the fibrous junction there can be observed, especially at the lateral aspect of the nerve bundles, where they abut on the endoneural connective tissue, similar fine black lines running longitudinally and in places sinuously, in close apposition to long spindle-shaped cells.

Amongst the general mass of degenerated fibres these young fibres are much less numerous.

PLATE 2.

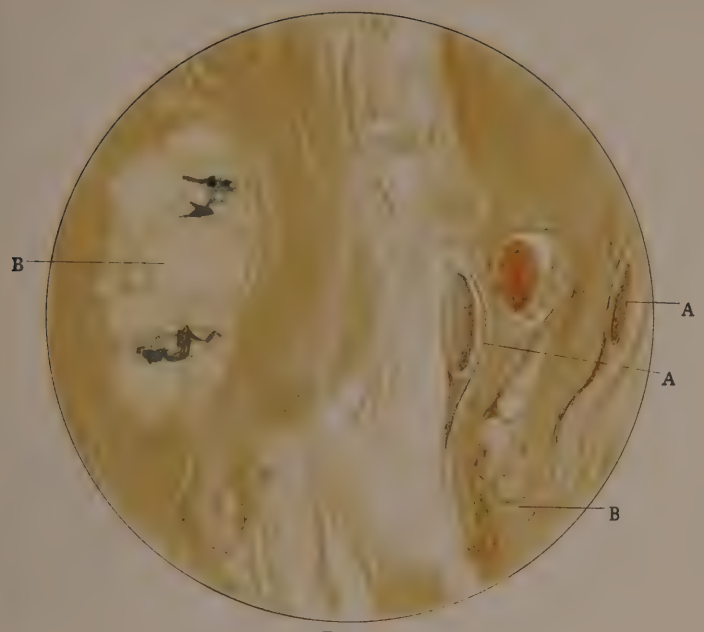


FIG. 5.

Dog. Sciatic. Divided and not sutured. 4 weeks.
To show the earliest stage of medullary sheath formation in distal segment (× 1000).
A.A. Fusiform cells with deposit of myelin along one side.
B.B. Globular degenerated remains of old sheaths.

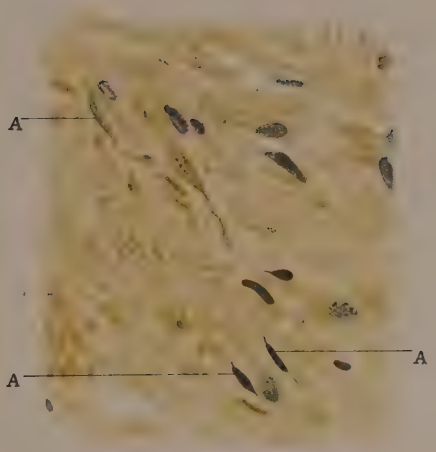
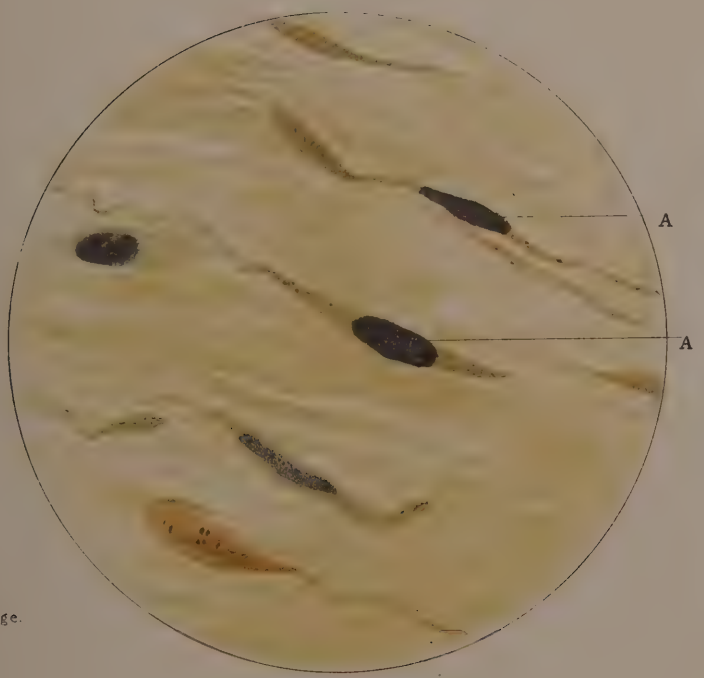


FIG. 6.

Monkey. Musculo-spiral. Divided and not sutured. 30 days.
To show early stage of myelin sheath formation in distal segment (× 300).
A.A. Spindle-shaped cells (neuroblasts) with deposition of myelin in each extremity.



H.Lapidge.

FIG. 7.

High power drawing of Fig. 6 (× 1000).
To show the deposit of myelin in the protoplasm of the neuroblasts as small discrete bodies.
A.A. Neuroblasts.

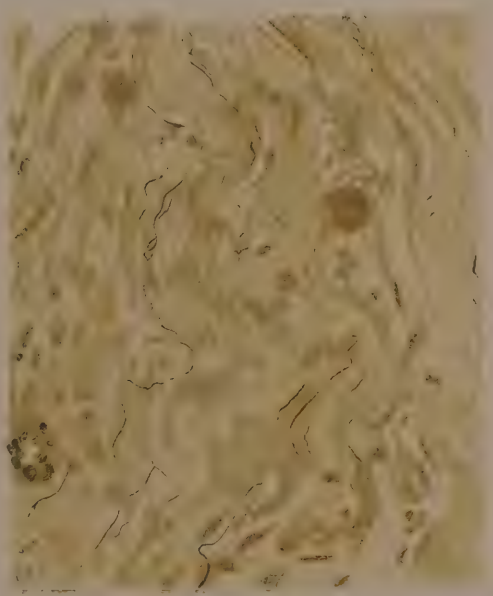


FIG. 8.

Dog. Sciatic. Portion of nerve excised. Ends left widely separated. 5 weeks.
To show young medullary sheaths developing in peripheral segment (× 300).

Observation 26

Dog. Sciatic nerve. Portion excised.
5 *weeks.*

The *proximal* segment is developing its advance-guard of new myelin sheaths, as described in previous specimens.

Some of the young sheaths are cut transversely, and are distinctly within the old neurilemmata.

In the *distal* part of the nerve fine embryonic myelin sheaths are present in great abundance, running sinuously between the rows of elongated nuclei. They are but faintly stained (see Plate 2, fig. 8).

Observation 27

Monkey. Median nerve. Divided in two places, half an inch apart, each division being at once sutured. (This is therefore equivalent to the transplantation or grafting of the intervening half-inch).
5 *weeks.*

Both in the *graft* and in the part of the nerve on the *distal* side of it young myelin sheaths are seen in process of formation as already described.

The myelin sheaths in the graft run irregularly. In the distal segment of the nerve they run longitudinally. They are more abundant in its cortex than in its centre.

In the nerve, two inches below the graft, long fine, slightly sinuous, black lines are to be observed. Here and there one overlaps another, forming undulating rows (see Plate 3, fig. 9).

Observation 28

Dog. Sciatic nerve. Half an inch of nerve excised and at once replaced by method already described.

$6\frac{1}{2}$ *weeks.*

(*a*) In upper end of graft.—Proximal stump is sprouting out its new myelin sheaths towards graft. Young sheaths are also forming in graft.

(*b*) In middle third of graft.—Young myelin sheaths are forming alongside spindle-shaped nuclei, and coursing in irregular masses in all directions. They are chiefly found in the immediate vicinity of blood-vessels (see Plate 3, fig. 11).

(*c*) In lower end of graft.—A suture is seen *in situ*; very large numbers of nucleated cells are present around both knots, much in excess of what is usually found around other sutures (probably asepsis not quite perfect). In the immediate vicinity of this cell-proliferation no new myelin sheaths can be detected, but in the distal portion of the nerve below the graft fine thread-like new sheaths can in places be seen.

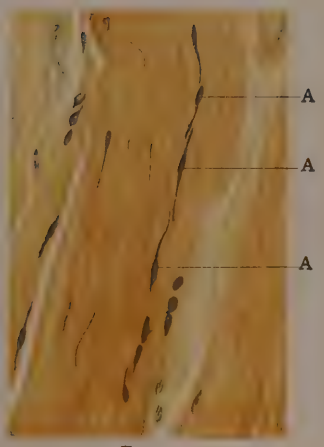


FIG. 9.

Monkey. Median. Immediate transplantation. 5 weeks.
To show, at a level two inches below the graft, the development of new medullary sheaths (× 200).
A.A.A. Imbricating series of young sheaths, the end of each overlapping its neighbour.

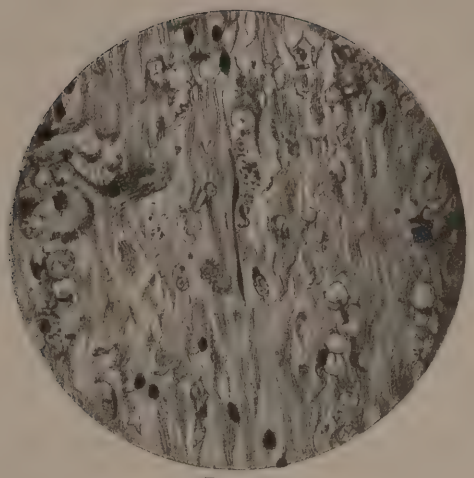


FIG. 10.

Cat. Sciatic. Divided and not united. 5 weeks.
Photograph of distal segment showing young medullary sheath in centre of field. Remainder of field consists of a mass of degenerated globules.

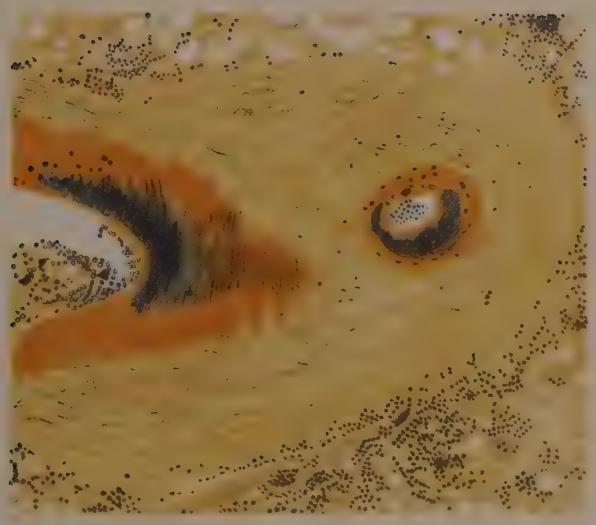


FIG. 11.

Dog. Sciatic. Immediate transplantation of ½ inch of nerve. 6½ weeks.
Drawing of section through middle third of graft. Two blood-vessels are seen in the field surrounded by large numbers of new myelin sheaths (× 100).

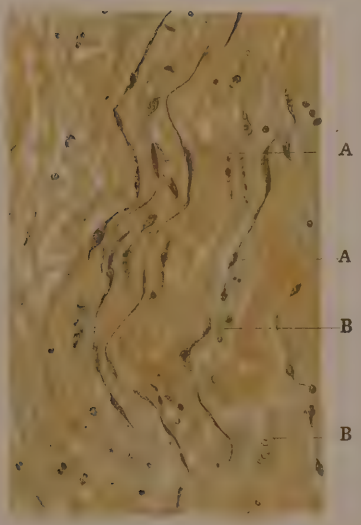


FIG. 12.

Dog. Sciatic. Immediate reunion. 8 weeks.
To show beaded myelin sheaths in peripheral segment (× 200).
A.A. Beaded sheaths.
B. Degenerated remains of old sheaths.

(*d*) Half an inch below graft.—Numerous fine hair-like young sheaths are in process of formation, and between them can be distinguished the profoundly degenerated and faintly-staining remains of the old myelin sheaths.

(*e*) Two, three, five, and six inches below graft.—Sections taken at all these levels show exactly similar appearances.

Young myelin sheaths are more abundant and are more easily demonstrated near the surface of the nerve-trunk than deeper in towards its centre.

Observation 29

Dog. Sciatic nerve. Divided and sutured immediately. 8 *weeks*.

As usual the *proximal* segment shows continuity of normal with fine young myelin sheaths. These latter are well stained. At first, above the scar-tissue, they are arranged longitudinally, then in the locality of the scar in an irregular plexiform manner, and finally, on the distal side of the scar, longitudinally again.

On the *distal* side, the young myelin sheaths are relatively more numerous in the superficial than in the central part of the tissue.

The young sheaths are now quite long and stain deeply ; they have a sinuous course, and well-marked fusiform and moniliform thickenings occur on them at intervals (see Plate 3, fig. 12).

Observation 30

Monkey. Ulnar nerve. Divided and not sutured.
10 *weeks.*
Fibrous junction occurred.

In the *proximal* segment young myelin sheaths are growing downwards towards the scar, but not perforating it.

In the intervening scar-tissue new myelin sheaths in small numbers are visible, much less advanced in development than those in distal segment, and wildly irregular in the directions they pursue.

On the *distal* side of the scar numerous fine, sinuous, hair-like sheaths can be detected, running longitudinally amongst the old degenerated myelin sheaths.

They are somewhat faintly stained (see Plate 4, fig. 13).

Observation 31

Dog. Sciatic nerve. Divided and immediately sutured.
12 *weeks.*

Regeneration is far advanced in the *distal* segment. The new myelin sheaths stain deeply. They are closely packed. Many of them approach normal adult sheaths in size (see Plate 4, fig. 14). They are, however, more sinuous in their course than normal ones. A thick medullary sheath nearing maturity appears to be formed by the fusion of a group of finer sheaths. A few scanty globular remains of

degenerated myelin sheaths can be made out amongst the new sheaths.

The intervening scar-tissue has the usual plexiform network of young myelin sheaths, but these are much less numerous than in the distal part of the nerve below the level of the suture. A suture can be seen *in situ* in the middle of this plexus of myelin sheaths.

Observation 32

Dog. Sciatic nerve. Divided and immediately sutured. 16 *weeks*.

(*a*) Half an inch above line of reunion.—Normal adult nerve.

(*b*) At site of reunion.—Regeneration is well advanced. The new myelin sheaths are deeply stained, but are not so large in diameter as normal nerve fibres.

(*c*) Half an inch below line of suture.—The appearances are similar to those already described in previous observations. In places the new myelin sheaths show distinct nodes, but at somewhat shorter intervals than is the case with the nodes of Ranvier in a normal nerve. The new nodes appear at first as dark rings or discs crossing the sheath transversely (see Plate 4, fig. 15).

Observation 33

A middle-aged woman accidentally divided her left ulnar nerve by cutting it with a pruning-knife. Anæsthesia and muscular atrophy resulted in the ulnar area.

Four months after the injury, the nerve was exposed above the anterior annular ligament. The bulb which had formed on the proximal stump was removed, together with the fibrous tissue below and a small part of the distal segment of the nerve. A portion of rabbit's sciatic nerve was sutured into the gap, so as to connect the proximal and distal ends.

The well-marked bulb at the lower end of the proximal segment is made up of dense connective tissue with large spindle-cells, and in apposition to the latter there are numerous young myelin sheaths.

In the dense connective tissue below, young myelin sheaths can be traced running in a plexiform manner in all directions.

In the distal segment of the nerve young myelin sheaths are again very evident, running sinuously and in parallel rows. The individual young sheaths have not yet linked on to each other to form continuous chains (see Plate 4, fig. 16).

Observation 34

1 cm. was removed from the musculo-spiral nerve of a monkey. $4\frac{1}{2}$ months later the intervening tissue, with portions of the proximal and distal ends attached, was excised, and in its place a portion of the sciatic nerve of a freshly killed rabbit was fixed by sutures.

FIG. 13.

Monkey. Ulnar. Divided and not sutured. 10 weeks. Distal segment.
To show new myelin sheaths (× 200).

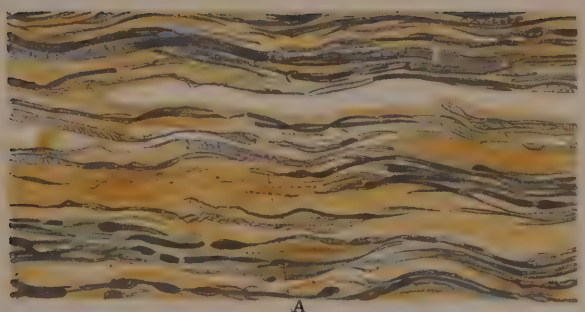


FIG. 14.

Dog. Sciatic. Divided and immediately sutured. 12 weeks.
To show regeneration of medullary sheaths in distal segment approaching maturity (× 300). Undulations scanty.
A. Group of fine medullary sheaths apparently fusing to form one large sheath.

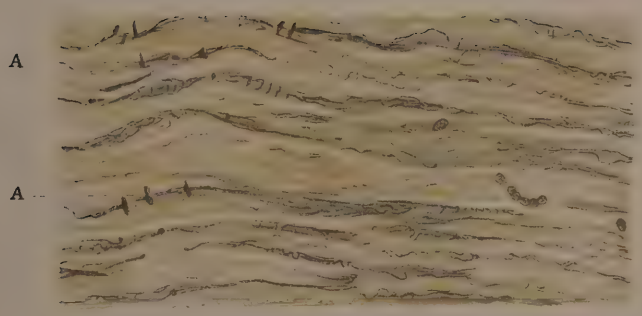


FIG. 15.

Dog. Sciatic. Divided and immediately sutured. 16 weeks.
To show discs (× 300) in the transverse diameter of the sheaths in distal segment.
A.A. Discs.

FIG. 16.

Man. Ulnar. 4 months after accidental division.
To show young sheaths in distal segment in the tubular plexus stage (× 200).

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The specimen was obtained ten days later.

In the *proximal* segment of the nerve, degeneration of the larger myelin sheaths is evident in the vicinity of the cut end. Leashes of new myelin sheaths are seen amongst the old, but they do not yet extend downwards beyond the limits of the old.

The *graft* itself is markedly degenerated, the myelin being broken up into globular masses taking the stain faintly.

In the *distal* part of the nerve fine hair-like young sheaths can be detected in places, running longitudinally amongst the old (compare Observation 26).

Observation 35

Monkey. Sciatic nerve. Divided, not sutured.
5 *months*.

The *proximal* segment terminates in a well-marked "bulb" formed of numerous leashes of young myelin sheaths coiled, intertwined, and bound together by fibrous tissue. The sheaths at the lowest part of the bulb run almost transversely to the long axis of the nerve.

In the *distal* segment of the nerve young myelin sheaths can be detected amongst the degenerated remains of the old.

A pad of muscle lies between the proximal and distal segments.

Observation 36

Dog. Sciatic nerve. Divided and sutured immediately.
5 *months.*

There is well-marked regeneration of the distal end. The myelin sheaths, however, are not so broad as those of the normal nerve on the proximal side of the lesion.

Observation 36a

A soldier in the Transvaal was wounded, by a Martini-Henry bullet, transversely through the back of the right thigh. Total paralysis, sensory and motor, of both external and internal popliteal nerves at once supervened, and though an attempt was made in Pretoria within a month after the injury to bring the ends of the nerves into apposition, no improvement had resulted up to the time when he came under our observation.

Nine months after the injury the sciatic nerve was exposed by one of us and was found to be completely severed. There was a gap of over four inches between the proximal and distal segments. The proximal segment was bulbous. The external and internal popliteal constituents of the distal segment were found separate from each other. They were not bulbous. The ends of the proximal and distal segments were rawed by removal of a small portion so as to present a fresh section of nerve-trunk. The intervening gap was then bridged over by the suturing in position of six inches of bullock's sciatic nerve so as to unite the segments both of the internal and of the external popliteal nerve, the grafts being in each case enclosed in decalcified bone-tubes. The

wound healed by first intention. At the time of writing this (five months after the operation), no return of sensory or motor functions had occurred.

On examination of the portions removed from the proximal and distal segments, copious new sheaths of small diameter are found in each of the *proximal* segments, coursing irregularly and sinuously in all directions in the end-bulb. The *distal* segment, in both cases, also shows a number of new sheaths, coiled and beaded. In the external popliteal the new sheaths are more numerous than in the internal. In both external and internal, new sheaths are most abundant in the loose superficial tissue of the nerve and scantiest in the core of the nerve-trunk, which is markedly fibrous in structure, and amongst this dense fibrous tissue the new sheaths are less developed as well as more scanty. In the distal segment of the internal popliteal an old silk suture is found to be embedded :—a relic of the first operation,—and there is marked proliferation of connective-tissue cells, as if it has been in a condition of interstitial neuritis.

Observation 36b

An officer received a Mauser bullet wound in the left arm at the battle of Colenso (December 15, 1899). Total paralysis, motor and sensory, of the ulnar nerve at once ensued, and was still present when he was operated on by one of us *eleven months* later. At the operation the ulnar nerve was found completely divided. There was a well-marked end-bulb on its proximal segment. The distal segment could not be brought within $1\frac{1}{2}$ inches of the proximal. Two inches of sheep's sciatic nerve were sutured into the gap.

Twenty days after the operation, some return of sensation, as tested with the Faradic battery, was observed in the little finger. Two months after the operation he could feel a pin-prick all over the ulnar area. Four months after the operation he could feel light touches all over, but there was still some impairment on the last phalanx of the little finger. Six months after the operation the anæsthesia had entirely disappeared, although the motor functions were still imperfect.

The *proximal* segment shows numerous bundles of young myelin sheaths interlacing in all directions, embedded in the fibrous tissue of the end-bulb.

In the *distal* segment there are abundant myelin sheaths narrower and more sinuous in outline than normal sheaths, and possessing moniliform thickenings in their course. Towards the upper end of the distal segment these new sheaths run very irregularly : lower down they are longitudinal in direction. No remains of the original degenerated sheaths can be detected.

Observation 37

A printer's cutter lost all the fingers of his left hand by an accident with the "guillotine." After the wounds healed considerable pain remained in the ulnar border of the hand, for which the nerve was divided by a surgeon above the wrist. In spite of this the pain persisted, and *thirteen months* after its operative division several inches of the nerve were excised by one of us, including the site of division and a portion of the nerve below, which had become attached by fibrous junction.

Examination of the *proximal* segment shows a well-developed "bulb" at its lower extremity. A few outlying processes containing myelin sheaths struggle down from the "bulb" towards the distal segment, but do not reach it.

The *distal* segment has no "bulb," but in it the myelin sheaths are fairly well regenerated, lying among degenerated sheaths and showing the beading characteristic of new sheaths.

A band of connective tissue intervenes between the proximal and distal segments of the divided nerve. In this fibrous tissue there is quite a long space in which no medullary sheaths are present.

COMMENTARY ON THE CHANGES OBSERVED IN THE MYELIN SHEATHS STAINED BY THE WEIGERT METHOD

At the end of twenty-four hours the extremity of the proximal segment (if left ununited) shows a mushroom-like appearance, which under the microscope is found to consist of recurved fibres separated in part by extravasated blood-corpuscles. This is the scaffold on which the "end bulb" of the proximal segment is afterwards built. We may therefore name it the "primitive end-bulb."

A. Degeneration

Apart from the traumatism of the operative procedure no true degeneration is observed until the fourth day, when commencing fragmentation of the myelin sheaths can be made out in the entire extent of the distal segment of the nerve.

This fragmentation is well marked on the fifth day, except in the finer sheaths in which this process begins a little later. By the seventh day, fine as well as coarse sheaths have become broken up.

The above remarks refer to changes in the cat's nerve. In Observation 15 the nerve of the monkey at the seventh day shows changes similar to those of the cat's nerve of the fifth day.

The further degenerative changes in the myelin sheaths of the distal segment can readily be followed. Week by week, the fragments of myelin take the stain less and less deeply, and become smaller from absorption and scantier in numbers. Ultimately the myelin remnants are taken into the substance of the invading cells, in whose protoplasm they can be distinguished as darkly staining particles at the end of the fifth month. Even at the thirteenth month in man, evidences of the same material, though more faintly stained, are still visible in the occasional clusters of cells between the new sheaths.

B. Regeneration

(1) *In nerves united as above described*

The earliest date at which any new sheaths are discoverable is at the end of the second week. They are developed in the *proximal* segment close above the plane of division.

The new sheaths lie not in the axis of the old sheaths, but excentrically and in close apposition to the cells of the neurilemma. The neurilemma cells do not share in the degenerative process.

The new sheaths are not outgrowths, branches, or continuations from the old sheaths of the normal nerve-fibre above. They are formed entirely apart from them. Tracing the process from

the plane of division upwards, small isolated groups of new sheaths are visible whose general direction is sinuously longitudinal. It is particularly to be observed that each group is an island which has, at first, no physical continuity with the peninsula of the normal medullary sheath above, to which, however, it is subsequently guided during its growth within the neurilemma tube.

At a higher level, adjacent islands of the same longitudinal series have become a continuous tubular plexus within the neurilemma, and higher still the plexus is continuous with the end of the normal sheath.

On the *distal* side of the plane of reunion no new myelin sheaths are visible at the end of three weeks, but at the end of four weeks they are to be seen in great abundance in the entire extent of the nerve. Many of the bundles of new myelin sheaths embrace the discrete globules which form the degenerated remains of the old.

It is important to observe that, whilst there are, at the end of four weeks, numerous new myelin sheaths both in the proximal and in the distal segment, they are relatively scanty in the intervening scar-tissue. The new sheaths at this date present a beaded appearance due to the occurrence on them of moniliform thickenings. The beads are produced by the presence of the cells from which the new sheath is produced.

The process of regeneration does not differ essentially from that which occurs in normal nerve, regeneration being a constant process in all tissues of the body. Thus in a normal nerve-trunk a few fine beaded sheaths may be observed amongst the overwhelming mass of adult sheaths, whereas the peripheral segment of a reunited nerve consists of numerous new sheaths,

the old ones being reduced to débris. When the sheath is young, as in regeneration at the end of four weeks, the cell bodies form prominent objects and hence the beaded appearance ; but as the sheath grows in size the neuroblast becomes less conspicuous, and finally can only be found at each internodal point. At the end of two months the beadings are still very conspicuous, but by the end of the third month they are reduced to undulations in consequence of the increasing width of the sheath. At the end of four months the diameter of the sheaths has further increased and their margins are less undulating. At the end of five months most of the new sheaths have reached the normal size and have lost their undulations, but show, relatively to a normal nerve, a greater proportion of small beaded sheaths.

In the *intervening scar-tissue* new sheaths are seen at the end of the fourth week. They are more numerous than in the adjacent portion of the central segment and much less abundant than in the distal segment. It cannot, therefore, be claimed that regeneration is a process of sprouting from the proximal segment, otherwise the new medullary sheaths would progressively diminish in number instead of increasing from above downwards. In the intervening scar-tissue the longitudinal arrangement of the new sheaths is lost. They interlace irregularly in all directions. Previous to the end of the fourth week no new sheaths can be observed in the scar-tissue.

(2) *In nerves divided and not sutured*

(*a*) *Changes in the proximal segment*

The development of the end-bulb.—As already described, a

"primitive end-bulb" is found at the end of the central segment within twenty-four hours after division of the nerve.

At the end of five weeks the permanent end-bulb is well advanced in development, the new sheaths forming a recurving spray like the apex of a fountain. Each new sheath is produced within the recurved neurilemma of an old sheath, the degenerated remains of which have become reduced by this time to the merest granular débris. At the end of five months the new sheaths have a distinctly beaded appearance. At the end of thirteen months they have not advanced beyond the beaded stage, though they have greatly increased in numbers. The beaded stage apparently is the limit of development in cases where functional conductivity is not re-established.

(*b*) *Changes in the distal segment*

In a nerve which has been completely cut off from all connection with the central segment new sheaths are first visible at the end of the fourth week. They appear as fine dark lines (see plate 2, fig. 5), each developing along one side of the protoplasm of a fusiform cell. The subsequent growth of the myelin sheaths is much slower than in the case of a reunited nerve and never gets beyond the beaded stage. Thus in a specimen obtained at the end of five months the beaded appearance is well seen. The two ends of the nerve happen to be separated by a pad of muscle, and in the distal segment the sheaths are long and beaded but few in number.

(3) *Transplantation experiments*

Of these only four were performed (Observations 34, 23, 27 and 28). Degeneration occurs in the graft exactly as in the distal segment of the divided nerve. The graft itself is a dead tissue, and is gradually absorbed and replaced, like blood-clot, by a living tissue.

At the end of four weeks the graft is degenerated, and there are no new myelin sheaths in its substance such as have been formed in the distal segment of the nerve-trunk below. But by the end of five weeks in the monkey numerous young myelin sheaths are present in the graft, chiefly in the neighbourhood of the in-growing blood-vessels. At six and a half weeks in the dog this is seen with still greater clearness (see Plate 3, fig. 11), and embryonic sheaths are visible in all parts of the graft.

The neuroblasts from which the embryonic sheaths are derived do not originally belong to the graft itself, but are to be numbered amongst the cells which invade and replace the graft from the distal as well as from the proximal segment. In immediate reunion the invaded part is a narrow zone, hence new sheaths are recognisable at the end of the fourth week, but in the broad zone of a half-inch graft new sheaths in the same stage of development are observed only at the end of six and a half weeks.

The invading neuroblasts travel into the graft alongside the blood-vessels, for the embryonic sheaths are found in greatest abundance in their immediate vicinity. This method of entrance facilitates nutrition of the actively growing sheaths, and is analogous to the process observed in the regeneration of any other specialised tissue.

PLATE 5.

Three weeks after Immediate Reunion.

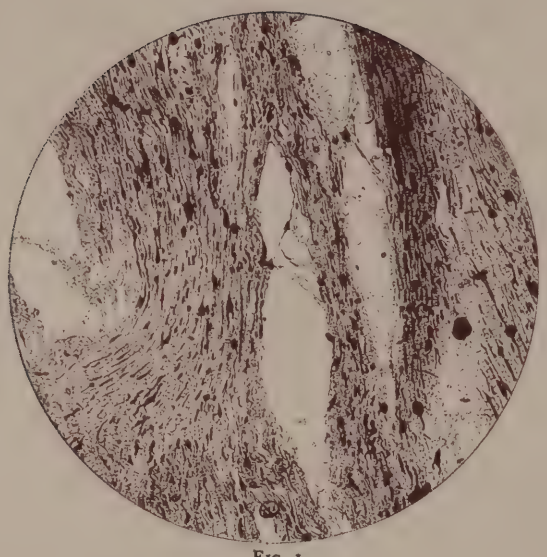


FIG. 1.

Photo of proximal segment at junction with intermediate scar-tissue (× 90). Axis-cylinders shown as numerous black lines coursing downwards into the scar-tissue.

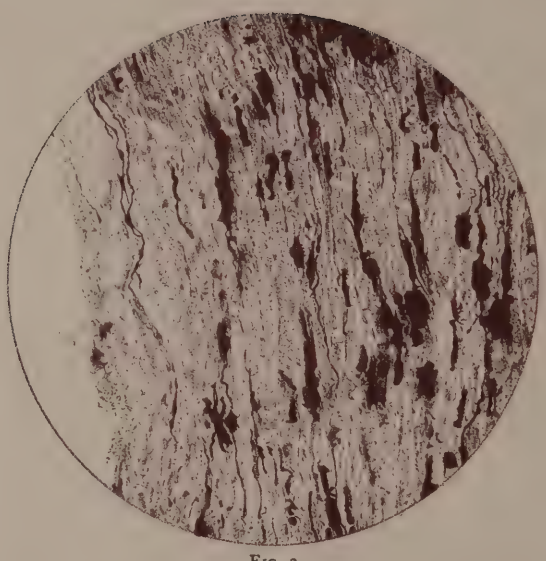


FIG. 2.

Photo (× 200) corresponding to the left upper quadrant of Fig. 1. A few spider-cells can be observed.

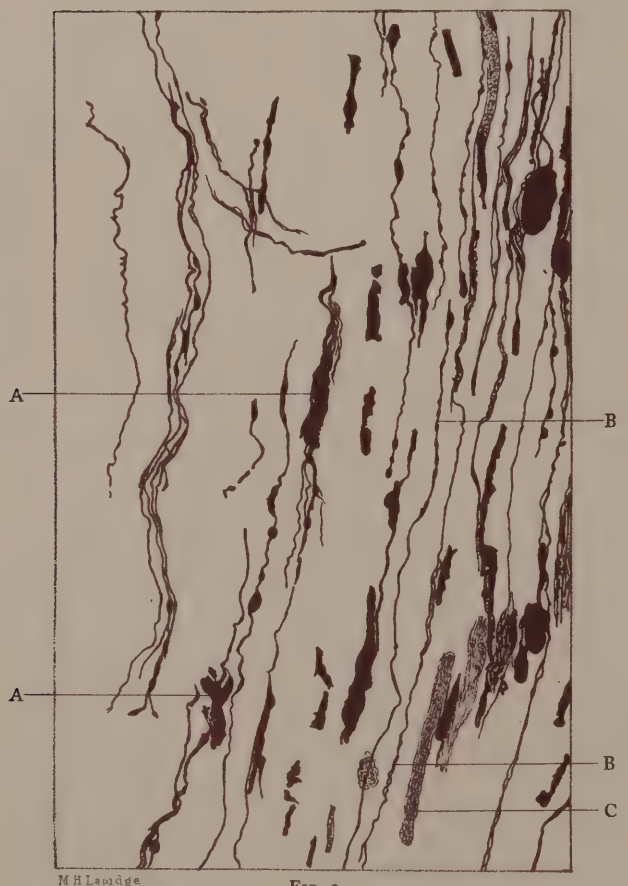


FIG. 3.

Drawing from same field as Fig. 2 (× 200).
A.A. Spider-cells.
B.B. Axis-cylinders.
C. Medullary sheath.

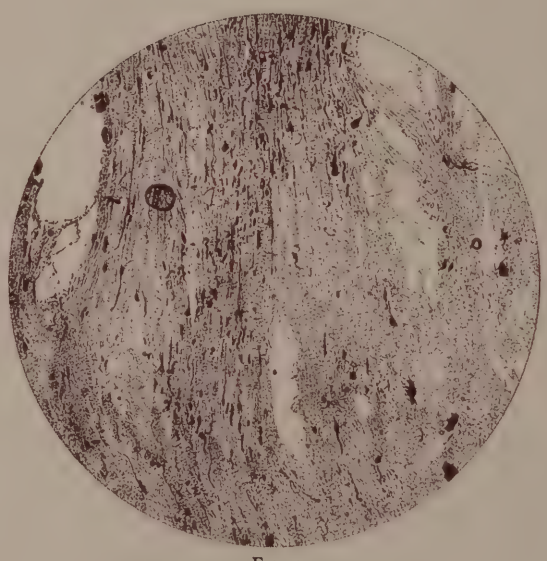


FIG. 4.

Photo of another section from proximal segment (× 90).

PLATE 6.

Three weeks after Immediate Reunion.

FIG. 5.

Higher power view of Fig. 4 of Plate 5 (× 200) near centre of upper part of field, showing degenerating axis-cylinders broken up into short lengths and fine new sinuous ones.

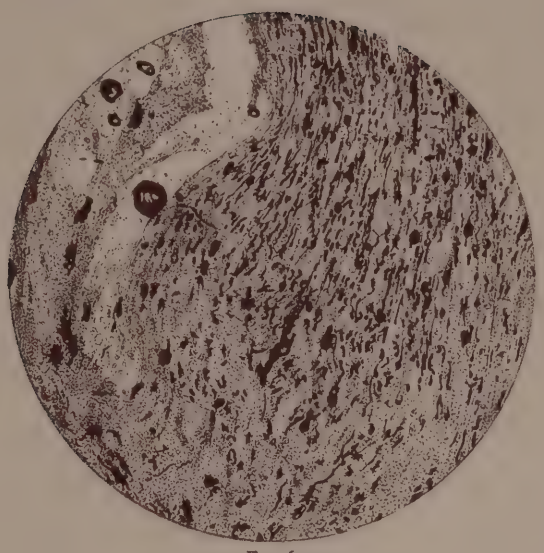


FIG. 6.

Photo (× 90). Similar appearances to Plate 5, Fig. 1.

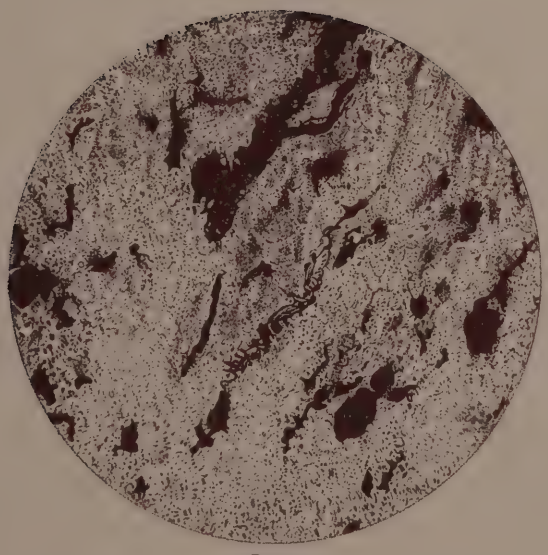


FIG. 7.

Photo (× 200). View of a portion of Fig. 6, just below centre. At upper part of field is a medullary sheath darkly stained. Below and to the right is a spiral convolution of young axis-cylinders.

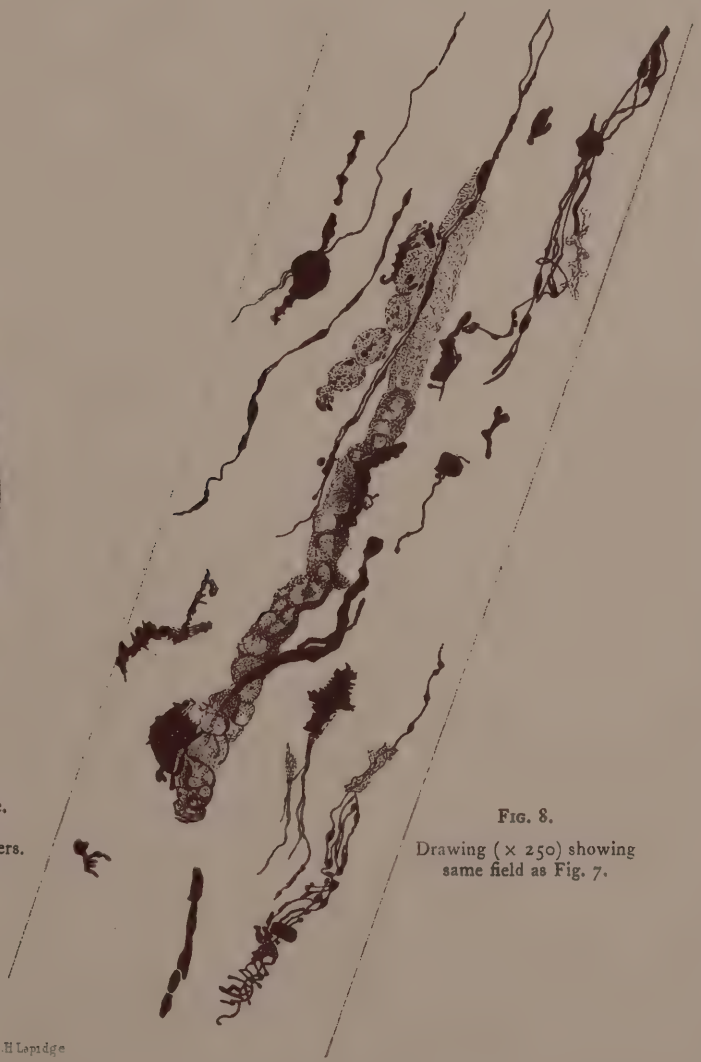


FIG. 8.

Drawing (× 250) showing same field as Fig. 7.

M.H.Lapidge

The graft is, therefore, a scaffolding invaded equally throughout its length by neurilemma cells from without, both from the proximal and from the distal segments. These enter alongside the blood-vessels, their path being the one of minimum resistance and of maximum nutrition.

CHAPTER III

THE AXIS-CYLINDERS

In the following series of observations the nerves were stained by the Golgi method. In successfully stained specimens the results are very striking, but success is difficult of attainment.

Observation 38

Cat. Sciatic. Divided and immediately sutured.
1 *week.*

The *proximal* segment shows axis-cylinders and a few "spider-cells": no "spider-cells" nor new axis-cylinders are present in the *intermediate tissue* nor in the *distal* segment. Here and there the remains of old axis-cylinders can be made out in the distal segment, but they are not nearly so black as normal axis-cylinders.

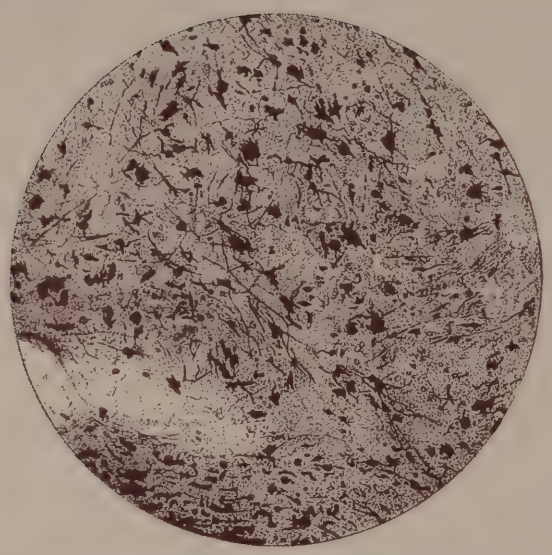
Observation 39

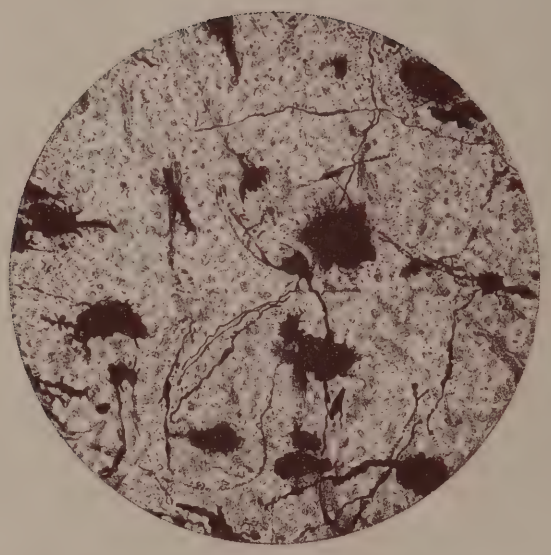
Cat. Sciatic. Divided and immediately sutured.
2 *weeks.*

The *proximal* segment shows axis-cylinders with "spider-cells" sparsely scattered amongst them.

PLATE 7.

Three weeks after Immediate Reunion.





FIGS. 9 and 10.

Photos of intermediate scar-tissue, low (× 90) and high power (× 200) respectively. Fig. 10 is midway between the centre and the upper margin of Fig. 9.

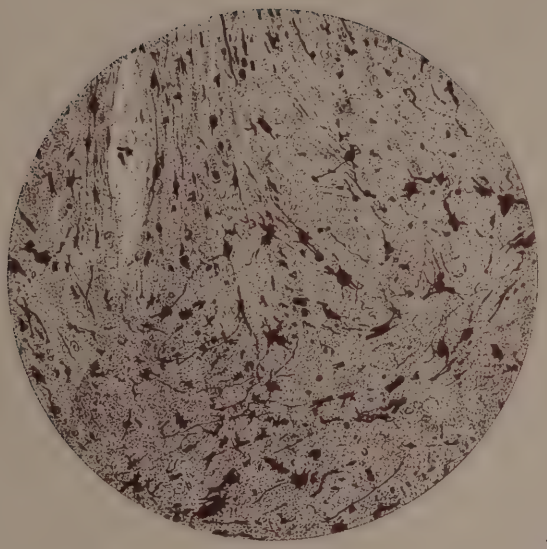
M H Lapidge

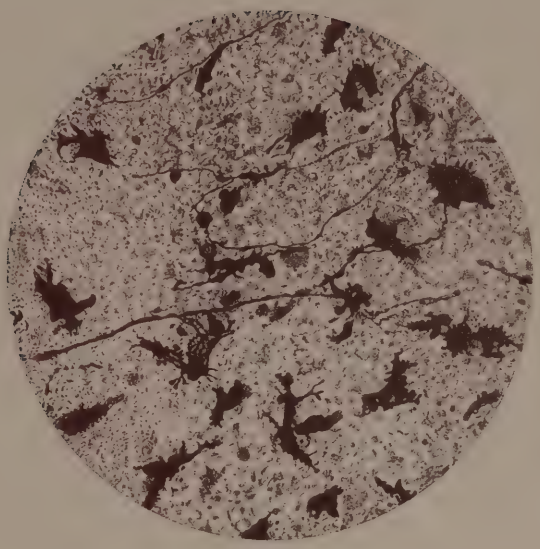
FIG. 11.

Drawing of same field as Fig. 10, showing "spider-cells" with long processes interlacing in all directions.

PLATE 8.

Three weeks after Immediate Reunion.





Figs. 12 and 13.

Photos of intermediate scar-tissue, low (× 90) and high power (× 200). The junction of the proximal segment with the scar-tissue is seen. Note spider-cells and their processes in the scar-tissue.
Fig. 13 is taken from the left lower quadrant of Fig. 12 near the middle line.

Fig. 14.

Photo of peripheral segment (× 90) showing numerous spider-cells with axis-cylinders growing out from both ends.

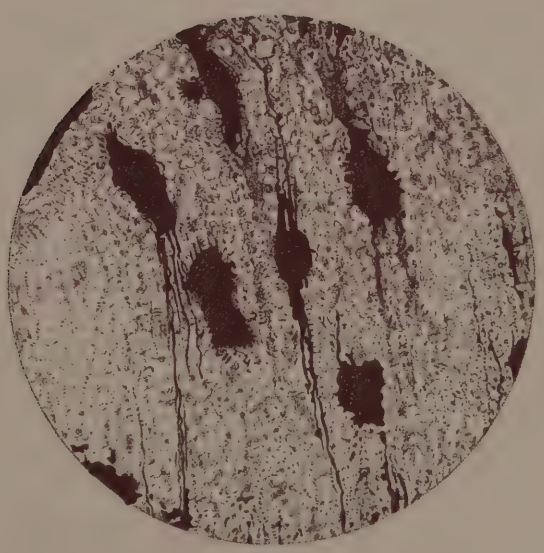


Fig. 15.

Photo (× 200) of a portion immediately above the centre of Fig. 14.

The *intermediate* scar-tissue shows neither axis-cylinders nor "spider-cells." The *distal* segment of the nerve shows a very few "spider-cells" with short projecting processes.

Observation 40

Cat. Sciatic. Divided and immediately sutured.
3 *weeks.*

Amongst the adult axis-cylinders at the most *proximal* end of the section (quite $\frac{3}{4}$ inch above the site of division) there are, in places, sparsely-distributed small cells from both ends of which young axis-cylinders project longitudinally. On tracing the adult axis-cylinders downwards towards the scar these "spider-like" cells become more numerously interspersed, and their processes longer (see Plates 5 and 6, figs. 1 to 8).

At the level of the scar the old axis-cylinders become less numerous and ultimately stop. Only a network of spider-cells is seen whose axis-cylinders cross and interlace in all directions (see Plates 7 and 8, figs. 9 to 13).

Below the scar the spider-cells are much larger and more numerous than on the proximal side, and numerous axis-cylinders grow out from both ends of each cell. The cells lie arranged in longitudinal rows, each cell with its long axis in the long axis of the nerve, and with its bundle of axis-cylinders projecting longitudinally from both ends.

The young processes from each cell in the periphery of the nerve overlap sometimes, but do not anastomose. The length of each process varies from one to six times the length of the parent cell; few are more than six times the cell length. Each process

ends in a somewhat club-shaped enlargement, and here and there shows slight thickenings in its course (see Plates 8, 9, and 10, figs. 14 to 19).

Observation 41

Cat. Sciatic. Divided and immediately sutured.
4 *weeks.*

"Spider-cells" are present amongst the adult axis-cylinders of the *proximal* segment, and these become more numerous as the intervening scar-tissue is approached (see Plate 10, figs. 20 and 21).

The *scar-tissue* itself is occupied by numerous interlacing processes of "spider-cells" (see Plates 10 and 11, figs. 22 to 25).

In the *distal* segment the processes from the "spider-cells" are markedly longer than at the end of three weeks. All the processes run longitudinally in the axis of the nerve trunk, and show small bulbous thickenings on them here and there.

The processes from different spider-cells are not continuous with each other (see Plates 11 and 12, figs. 26 to 29).

Observation 41a

An officer at the battle of Magersfontein (December 11, 1899) received a Mauser bullet wound through the back of the right leg, severing the external saphenous nerve. Anæsthesia resulted in the corresponding area of skin on the outer aspect of the foot.

Ten months later the nerve was exposed by one of us, and was

PLATE 9.

Three weeks after Immediate Reunion.

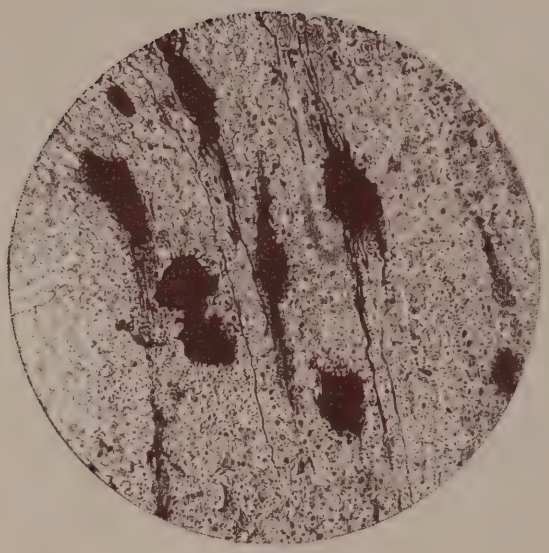


FIG. 16.

Photo (× 200). Same field as Fig. 15 of Plate 8, but at a different focus. Figs. 15 and 16 show the spider-cells with their long axis-cylinder continuations. The dots in the ground-work are due to a precipitate during the Golgi process. The dumb-bell-shaped mass from which no processes arise is an artefact.

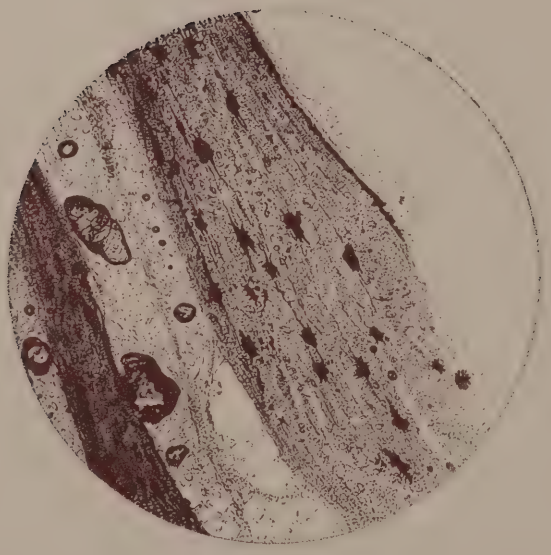


FIG. 18.

Photo of peripheral segment (× 90). Similar appearances as in Fig. 14, Plate 8.

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FIG. 17.

Drawing (× 200) of same field as Figs. 15 and 16, but the processes are traced to their terminations.

PLATE 10.

Fig. 19—*Three weeks after Immediate Reunion.*

Figs. 20, 21, 22—*Four weeks after Immediate Reunion.*

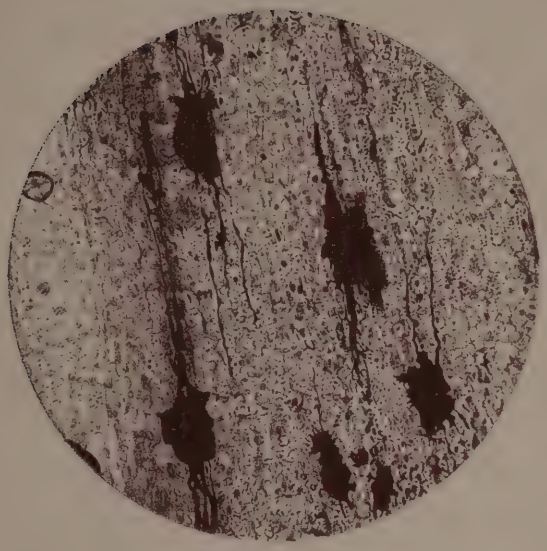

FIG. 19.

Photo (× 200). Portion of same field as Fig. 18, just to left of centre.

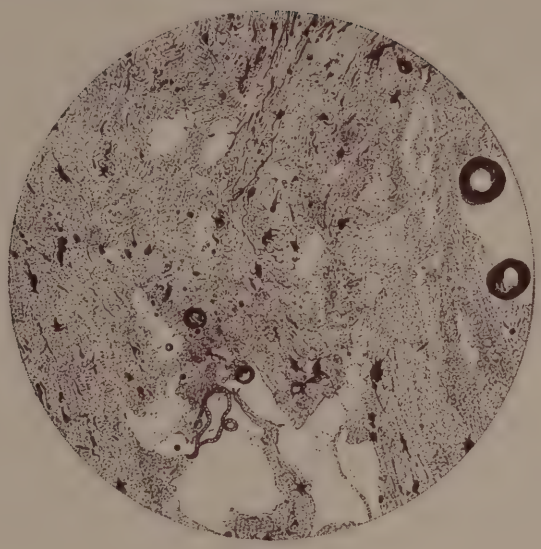

FIG. 20.

Photo of proximal segment (× 90) at junction with intermediate scar-tissue. Spider-cells more numerous than in similar situation at three weeks.

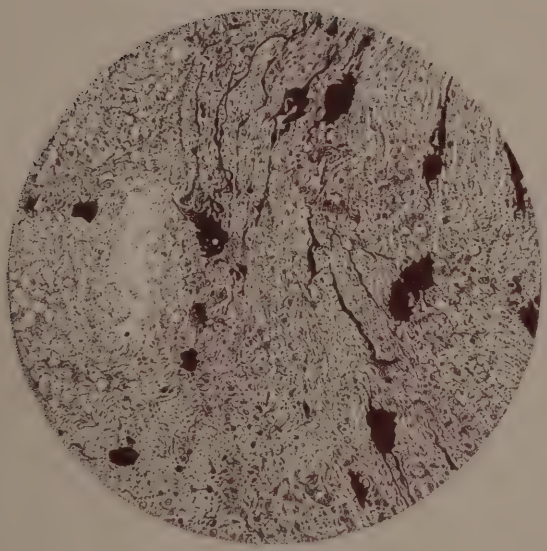

FIG. 21.

Photo (× 200) at centre of same field as Fig. 20. Shows spider-cells.

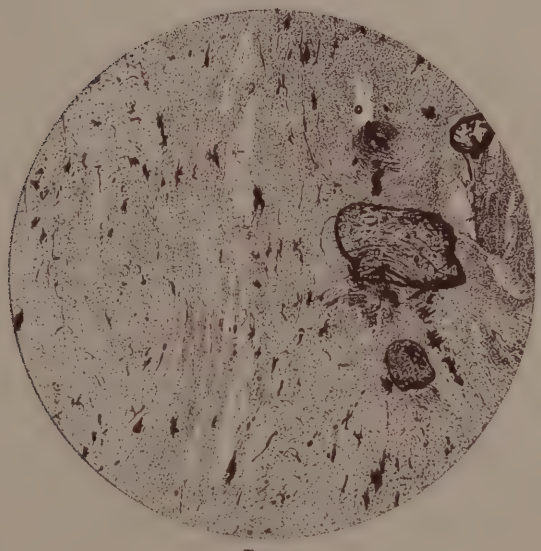

FIG. 22.

Photo of intermediate scar-tissue (× 90). Ligatures seen *in situ*. The large dark-edged area between the pieces of silk is an artefact, so also is the one below the lower piece of silk. The photo shows numerous spider-cells.

found embedded in the scar-tissue of the bullet track. Its proximal and distal segments were widely separated, and, even after dissection from the surrounding structures, could not be brought within an inch of each other. The gap between the two segments was bridged across by the insertion of $1\frac{1}{2}$ inches of a kitten's sciatic nerve.

In the portion of the proximal segment removed at the operation numerous axis-cylinders are present, both old and new, the latter interlacing irregularly near the free end of the segment.

In the distal segment a few axis-cylinders are seen, much less abundant than in the proximal segment. They are distinctly beaded, and, here and there, the end of one axis-cylinder overlaps the end of its neighbour. No large "spider-cells" are visible.

COMMENTARY ON THE REGENERATION OF AXIS-CYLINDERS STAINED BY THE GOLGI METHOD

These specimens present a striking confirmation of the results obtained by the Weigert method.

In the normal nerve prepared by the Golgi method a few "spider-cells" can be seen, scantily distributed. When the nerve is divided the earliest stage of regeneration first occurs in the lower end of the proximal segment at the end of the second week, and consists in an increase in the number of the "spider-cells." In the intermediate scar-tissue at this date no axis-cylinders or spider-cells can be distinguished, but at the end of the third week both in the scar-tissue and in the distal segment regenerative changes are well marked. In the proximal segment the processes

of the "spider-cells" run longitudinally; in the intermediate scar-tissue they form a delicate interlacing network, and in the distal segment they are both larger and more numerous than in the proximal segment, and are arranged with longitudinal parallel processes growing out from opposite ends of each cell. They approach the processes of the next cell of the same longitudinal series, but do not anastomose.

At the end of the fourth week the processes of the "spider-cells" in the distal segment are much longer than at three weeks, but do not yet anastomose, though they often overlap.

It is clear, then, that the regeneration of the axis-cylinders does not take place by a process of outgrowth from the proximal segment, but is commenced and completed by the activity of cells already existing in the trunk of the nerve.

PLATE 11.

Four weeks after Immediate Reunion.

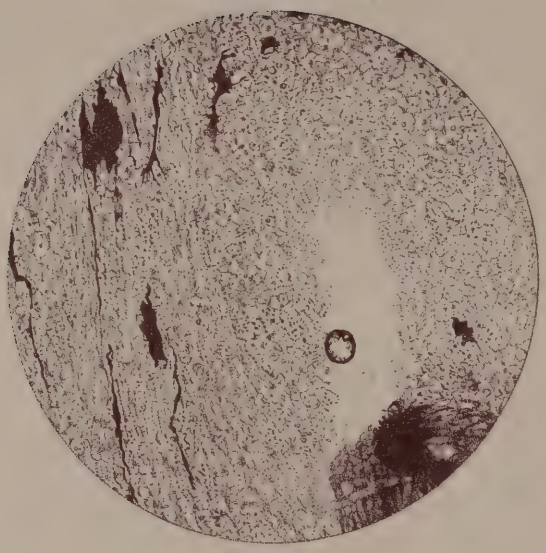

FIG. 23.

Photo (× 200). Right upper quadrant of Fig. 22.
Shows spider-cells and processes, also portion of silk ligature at lower margin of field.

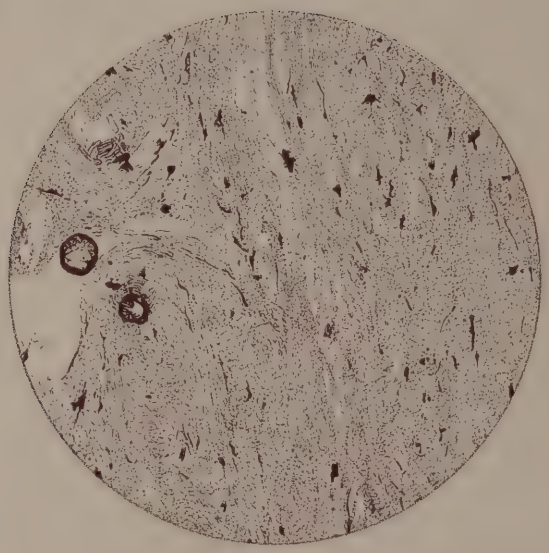

FIG. 24.

Photo of intermediate scar-tissue (× 90). Ligatures seen *in situ*.
Numerous spider-cells.

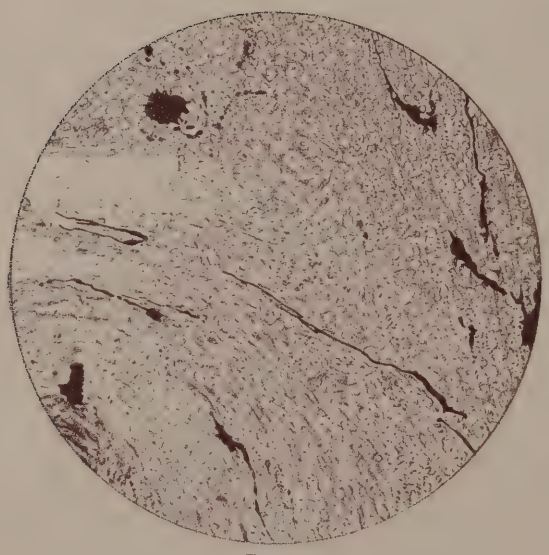

FIG. 25.

Photo (× 200) at junction of left upper and lower quadrants of Fig. 24.

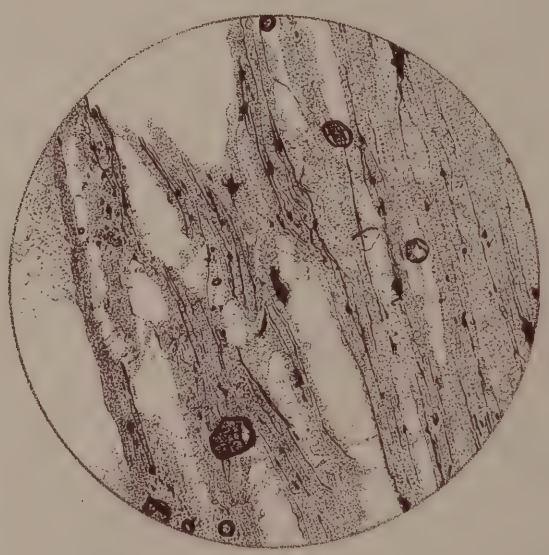

FIG. 26.

Photo of distal segment (× 90), showing spider-cells with processes many times longer than at three weeks.

PLATE 12.

Four weeks after Immediate Reunion.

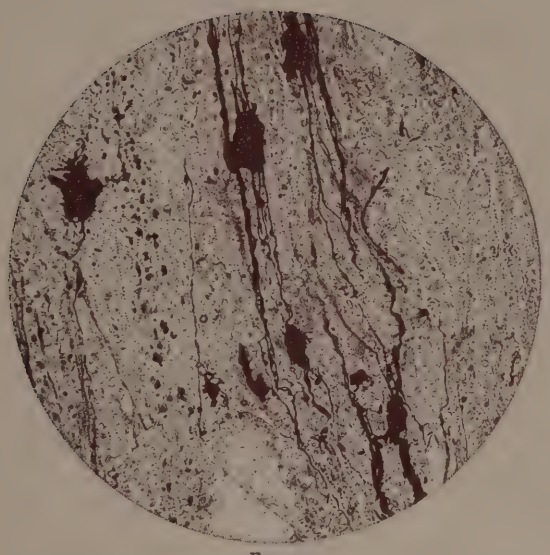

FIG. 27.

Photo (× 200). Portion of field of Fig. 26 above the centre. Shows spider-cells with axis-cylinder processes. The latter have bulbous swellings.

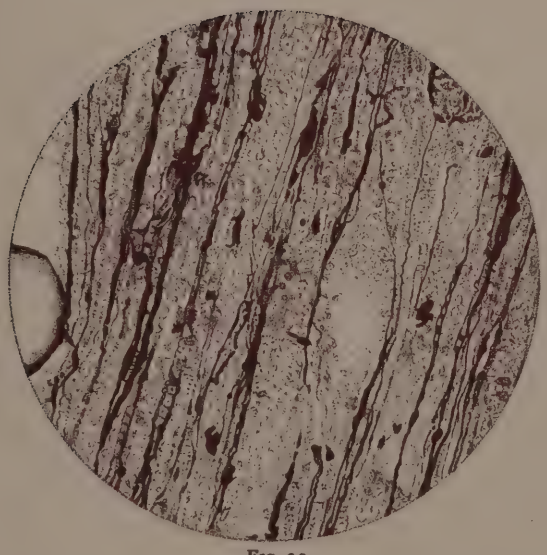

FIG. 29.

Photo of distal segment (× 200) showing numerous new axis-cylinder processes and a few spider-cells. Contrast Fig. 14 of Plate 8 (three weeks).

FIG. 28.

Drawing of distal segment (× 130). Same field as Fig. 27, but traced further. Compare length of axis-cylinder processes at three weeks (see Fig. 17 of Plate 9).

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CHAPTER IV

THE AXIS-CYLINDERS (*continued*)

THE following series of observations were made upon nerves stained by Stroebe's method for differentiation of the axis-cylinders. This stain is somewhat uncertain in its results, hence only a portion of the sections were useful for study. In sections where the stain has been successful the results are striking, the axis-cylinders staining an intense blue, the background being pink. Those specimens in which the stain failed to satisfactorily differentiate the axis-cylinders were excluded from this series.

OBSERVATION 42

Cat. Sciatic. Divided, not sutured.
12 *hours*.

Proximal segment.—The axis-cylinders terminate in clubbed extremities a short distance within the cut ends of the medullary sheaths.

Observation 43

Cat. Sciatic. Divided, not sutured.
24 *hours.*

Proximal segment.—The nerve-fibres are arranged in a "mop" (compare Observation 3 and Plate 1, fig. 1). The clubbed ends of the axis-cylinders terminate within the medullary sheaths.

Observation 44

Cat. Sciatic. Divided, not sutured.
24 *hours.*

Distal segment.—At the superficial edge of the section the medullary sheaths have been somewhat altered by the Flemming's solution in which they were fixed, and show very clearly the so-called "funnels" of Rezzonico and Golgi.

Observation 45

Cat. Sciatic. Divided and immediately sutured.
2 *days.*

In the immediate vicinity of the wound the axis-cylinders both of the proximal and distal segments are broken down; but at a little distance from the seat of injury they stain normally, both in proximal and distal segments.

Observation 46

Cat. Sciatic. Divided and not sutured.
2 *days.*

Proximal segment.—The axis-cylinders, both large and small, terminate in bulbous ends, like Indian clubs, close to the cut end, as already described.

There is some blood extravasation between and within the medullary sheaths.

Observation 47

Cat. Sciatic. Divided and not sutured.
2 *days.*

Distal segment.—The axis-cylinders below the level of the wound stain normally. No breaking of continuity has yet occurred.

Observation 48

Cat. Sciatic. Divided and immediately sutured.
3 *days.*

Both on *proximal* and *distal* sides of the wound the axis-cylinders stain normally.

Observation 49

Cat. Sciatic. Divided and not sutured.
3 *days.*

Proximal segment.—The axis-cylinders stain normally. Close to the site of division, here and there, pieces of

detached axis-cylinder are seen coiled up within the medullary sheaths.

Observation 50

Cat. Sciatic. Divided and not sutured.
3 *days*.

Distal segment.—The axis-cylinders stain well.

Observation 51

Cat. Sciatic. Divided and immediately sutured.
4 *days*.

On the *distal* side of the plane of reunion, the axis-cylinders are broken up here and there into irregular masses. The great majority, however, do not yet show any change.

Observation 52

Cat. Sciatic. Divided, not sutured.
4 *days*.

Proximal segment.—Practically the same appearances as in the three days' specimen.

Observation 53

Cat. Sciatic. Divided and not sutured.
4 *days*.

Distal segment.— Many axis-cylinders are still uninjured. The breaking-down ones, however, are somewhat more numerous and scattered indifferently through the section. They are equally distributed at the upper and at the lower end of the section.

Observation 54

Cat. Sciatic. Divided and immediately sutured.
5 *days.*

In the *proximal segment* the axis-cylinders are normal until reaching the vicinity of the wound, where they terminate in swollen ends.

On the *distal* side of the wound some axis-cylinders still stain almost normally, but most of them are interrupted and irregular in diameter, swollen here and there. They are sometimes coiled up within the medullary sheaths, which are in a state of fragmentation.

The finest axis-cylinders have remained unaltered the longest (compare Observation 10).

Observation 55

Cat. Sciatic. Divided and not sutured.
5 *days.*

Proximal segment.—The axis-cylinders come close down to the wound and terminate in Indian-club-like enlargements.

Observation 56

Cat. Sciatic. Divided and not sutured.
5 *days.*

Distal segment.—All the axis-cylinders are broken up into short lengths or globules within the fragmented medullary sheaths.

Observation 57

Cat. Sciatic. Divided and immediately sutured.
6 *days.*

On the *distal* side of the plane of division most of the axis-cylinders are broken down and confluent with the globules of myelin which stain irregularly blue; here and there, however, a length of axis-cylinder still remains, very irregular in its diameter, threading its way through the fragmented myelin.

Observation 58

Cat. Sciatic. Divided and not sutured.
6 *days.*

Proximal segment.—The axis-cylinders close to the cut end are broken up into globules and into irregular masses confluent with the myelin.

Observation 59

Cat. Sciatic. Divided and not sutured.
6 *days*.

Distal segment.—The axis-cylinders are mostly broken up and confluent with the myelin sheaths. Here and there, however, a considerable length of axis-cylinder still preserves its continuity, threading its way through the breaking-down myelin.

Observation 60

Cat. Sciatic. Immediate transplantation as in Observation 27.
6 *days*.

Changes in the nerve above and below the graft are the same as already described in non-united nerve of the same date.

The graft itself has its axis-cylinders broken up: they stain much more faintly than in the distal segment of the nerve below.

Observation 61

Cat. Sciatic. Divided and immediately sutured.
1 *week*.

In the *proximal* segment, near the wound, numerous small axis-cylinders are interspersed amongst the broken-down larger ones. They differ in appearance from newly-formed axis-cylinders by their absence of sinuosity and their coarser diameter.

In the *distal* end, the axis-cylinders and myelin sheaths are confluent and broken up into irregular blue-staining masses.

Here and there in the centre of such a mass a portion of axis-cylinder can still be made out.

Observation 62

Cat. Sciatic. Divided and not sutured.
1 *week.*

Proximal segment.—The axis-cylinders, as they approach the cut end, become irregularly swollen and terminate in bulbous ends.

No new fibres can be seen in process of formation.

Observation 63

Monkey. Musculo-spiral. Divided and not sutured.
1 *week.*

Proximal segment. — The appearances are similar to those in the cat's nerve of same date. The neurilemma nuclei are more easily seen than in the cat's nerve.

Observation 64

Cat. Sciatic. Divided and not sutured.
1 *week.*

Distal segment.—There is extensive breaking up of axis-cylinders and medullary sheaths into irregular elongated masses. The medullary sheath and axis-cylinder of each degenerated fibre are confluent and stain as one blue mass.

Here and there the finer axis-cylinders survive longer than those of larger diameter (see Plate 13, fig. 1).

Observation 65

Monkey. Musculo-spiral. Divided and not sutured.
1 *week.*

Distal segment.—The appearances are similar to those in the cat's nerve, viz:—breaking up of sheaths and axis-cylinders. The proliferation of the nuclei of the neurilemma is specially well seen (better than in the cat). The proliferated nuclei lie with their long axes parallel to the fibres.

Observation 66

Cat. Sciatic. Divided and not sutured.
2 *weeks.*

Distal segment.—The medullary sheaths are completely broken up. Here and there they contain deep blue masses in which occasionally, when of some length, the old axis-cylinder can be made out, coiled up and swollen irregularly; elsewhere they contain merely dark blue globules, and not always these.

Interspersed between the masses of myelin are numerous elongated cells, with rod-shaped nuclei parallel to the long axis of the nerve. They are best seen where the section has become frayed out.

No new axis-cylinders can be made out.

Observation 67

Cat. Sciatic. Divided and immediately sutured.
2 *weeks.*

On the *proximal* side of the plane of reunion new axis-cylinders are present near the cut end, forming alongside elongated nuclei.

The *distal* segment is made up of a close network of elongated cells lying parallel and longitudinally. Interspersed amongst these are the broken-down remains of the old sheaths with a few blue-staining remnants of axis-cylinder here and there inside.

The structure of the distal segment is best seen where the section is somewhat frayed.

No new axis-cylinders are present in the distal segment.

Observation 68

Cat. Sciatic. Divided and not sutured.
2 weeks.

Proximal segment.—At the lower end, beyond the last swollen extremities of the old axis-cylinders and medullary sheaths, isolated fine blue lines can be seen, each lying in apposition to an elongated nucleus, thickest in the vicinity of a nucleus and tapering away at each end. These occur at some distance below the lowest limit of the old axis-cylinders, and separated by a distinct space from them (see Plate 13, figs. 2 and 3).

Slightly higher up the nerve, new axis-cylinders are also in process of formation.

Nowhere are they seen sprouting out from an old axis-cylinder. Numerous places occur where young axis-cylinders are being formed as imbricating lines, thicker near the centre and tapering away where they overlap. Many such lines are formed in connection with a single neurilemma.

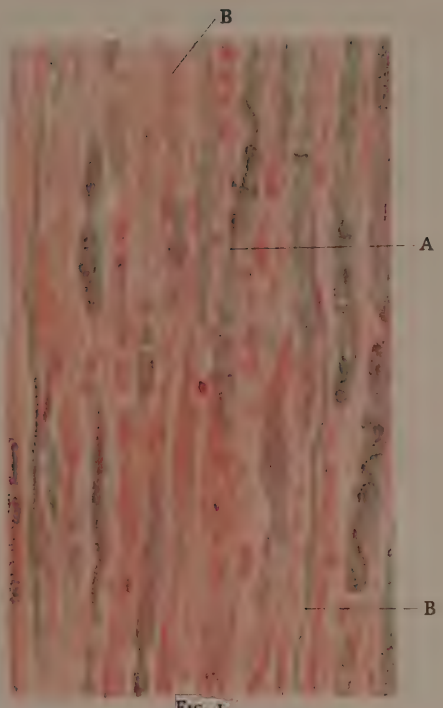

FIG. 1.

Cat. Sciatic. Divided and not sutured. 1 week. Distal segment. To show degeneration of the fibres. The medullary sheaths, unlike normal sheaths, stain blue. The darker lines within them are the broken-up axis-cylinders. Some of the smaller axis-cylinders remain undegenerated (× 300).

A. Degenerated fibre.

B. Undegenerated axis-cylinders.

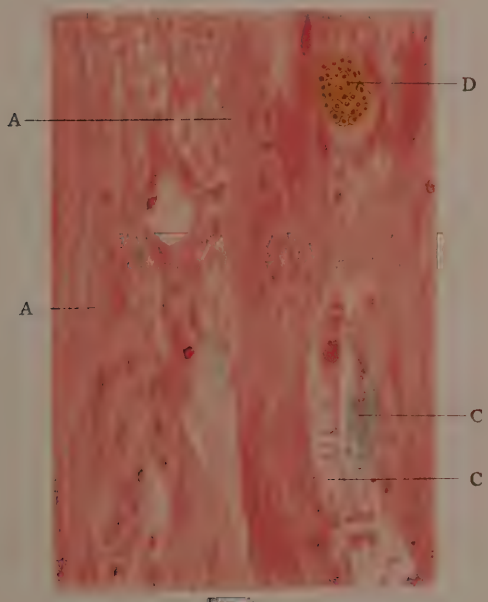

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FIG. 3.

Cat. Sciatic. Divided and not united. 2 weeks. Proximal segment (× 300).

A. Young axis-cylinder.

C. Degenerated fibres.

D. Blood-vessel.

FIG. 2.

Cat. Sciatic. Divided and not sutured. 2 weeks. Proximal segment (× 200).

To show formation of new axis-cylinders as small islands separated by wide intervals from the central axis-cylinders.

A. Young axis-cylinders.

B. Central axis-cylinders.

Observation 69

Monkey. Median. Portion excised.
20 *days.*

In the *proximal* segment fine blue threads can be detected lying longitudinally amongst the long nucleated cells.

In the *distal* segment here and there a fragment of axis-cylinder is coiled up within a portion of medullary sheath. The great mass of the distal segment, however, is made up of closely-packed, longitudinally-arranged chains of nucleated cells. Even where the section is frayed out, no new axis-cylinders can be seen forming along these chains.

Observation 70

Cat. Sciatic. Divided and immediately sutured.
3 *weeks.*

On the *proximal* side of the wound new axis-cylinders are forming as already described.

In the *distal* segment, especially at the periphery of the nerve, here and there fine blue lines are seen lying alongside elongated nuclei.

The old axis-cylinders and medullary sheaths are completely broken up, forming irregular masses between rows of elongated cells (see Plate 14, fig. 4).

Observation 71

Cat. Sciatic. Divided and not sutured. Fibrous junction occurred.

3 *weeks.*

In the *proximal* segment new fibres are forming as usual. No new fibres are seen in the *distal* segment. In a section of the distal segment half an inch below the plane of division, the myelin is broken up into coarse globules, some of which stain irregularly blue. Remnants of old axis-cylinders can here and there be made out within such myelin masses.

Observation 72

Dog. Sciatic. Divided and not sutured.

4 *weeks.*

Proximal segment.—New nerve fibres are forming at the lower end, but much more scantily than in the cat's nerve of an earlier date.

Distal segment.—Here and there, amongst the broken-up myelin globules, fine longitudinal wavy lines are seen, each in apposition to an elongated nucleus.

Observation 73

Cat. Sciatic. Transplantation of a portion 8 mm. long.

4 *weeks.*

The *proximal* segment shows new axis-cylinders forming in abundance.

There are no new axis-cylinders in the *graft*, which is completely degenerated.

In the *distal* segment, below the graft, fine wavy lines can be traced, running longitudinally between the broken-up masses of myelin.

Observation 74

Cat. Sciatic. Divided, not sutured. Fibrous junction occurred.

5 *weeks*.

There is a well-marked end-bulb at the lower end of the *proximal* segment. In this, new axis-cylinders are forming alongside spindle-shaped nuclei as usual.

No axis-cylinders occur in the dense *intervening fibrous tissue*.

In the *distal* segment, the degenerated globules of old fibres are packed, faintly stained, between longitudinal rows of elongated cells. Here and there fine blue lines can be traced running longitudinally from the extremities of these spindle cells (see Plate 14, fig. 5).

Observation 75

Monkey. Musculo-spiral. Divided, not sutured.

5 *weeks*.

In the *distal* segment, here and there, well-marked new axis-cylinders, sinuous in outline, are lying amongst the proliferated nuclei of the neurilemma (see Plate 14, fig. 6).

Observation 76

Dog. Sciatic nerve. A portion was excised. Three weeks later, $4\frac{1}{2}$ cm. of cat's sciatic inserted into gap, after rawing the upper and lower ends.

Specimen obtained $6\frac{1}{2}$ *weeks* later.

In the graft itself new blood-vessels occur, around which numerous spindle-cells are present.

Distal segment.—Some fine young blue fibres can be seen, forming wavy lines amongst the elongated nuclei.

Observation 77

Dog. Sciatic. Divided and immediately sutured.
8 *weeks.*

In the *distal* segment numerous new fibres can be detected, beaded in outline, lying in close apposition to the proliferated neurilemma nuclei and forming long sinuous blue lines. The degenerated masses of old myelin are interspersed here and there among the longitudinal rows of nuclei (see Plate 14, fig. 7).

Observation 78

Dog. Sciatic. Divided and immediately sutured.
12 *weeks.*

In the *distal* segment, close to the plane of reunion, new axis-cylinders are present, still sinuous, but now separated from the

neurilemma nuclei by a distinct interval, probably occupied by the new medullary sheath.

Lower down this is seen still more clearly.

Observation 79

Dog. Sciatic. Divided and immediately sutured.
16 *weeks*.

Distal segment.—Similar appearances to twelve weeks' specimen, but the new axis-cylinders are broader in diameter.

Observation 80

Human ulnar.
4 *months* after accidental division.

The *proximal* segment shows a well-marked bulb with new fibres in it.

The *distal* end shows new fibres, fine and sinuous, in close apposition to nuclei, and much smaller in diameter than in a reunited nerve of the same date in the dog.

Observation 81

Monkey. Median nerve. 1 cm. excised. 4 months later the fibrous tissue between the two ends, together with a small portion of both proximal and distal segments, was excised and a piece of fresh sheep's sciatic nerve 8 mm. in length was sutured in position.
Specimen obtained 5 *weeks* later.

Proximal segment.—New fibres forming at lower end.

In the graft.—No new fibres. It is infiltrated with large numbers of round cells.

Distal segment.—Fine blue lines forming alongside spindle-shaped nuclei.

Observation 82

Monkey. Median nerve. Divided, not sutured.
5 *months.*

Distal segment.—Numerous sinuous fibres can be made out between the proliferated elongated nuclei.

Observation 83

Monkey. Musculo-spiral. Divided, not sutured.
5 *months.*

Sinuous fibres are present in the *distal* segment in great abundance, as in Observation 82.

Observation 84

Dog. Sciatic. Divided and immediately sutured.
5 *months.*

Distal segment.—Well-marked regeneration. The new fibres are here and there separated from the neurilemma nuclei by a distinct margin, probably corresponding to the medullary sheath (see Plate 14, fig. 8).

Observation 85

Human ulnar.
13 *months after division* (see Observation 37).

Two inches and 1 *inch above division:*—Amongst the normal

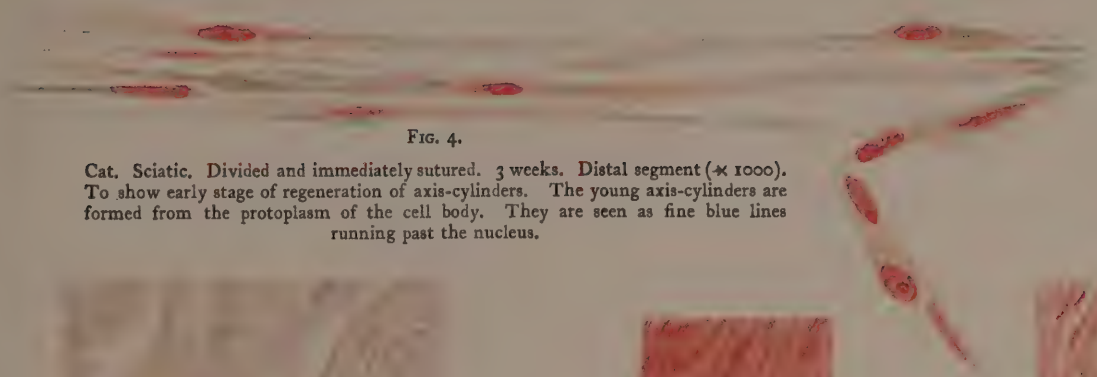

FIG. 4.

Cat. Sciatic. Divided and immediately sutured. 3 weeks. Distal segment (× 1000).
To show early stage of regeneration of axis-cylinders. The young axis-cylinders are formed from the protoplasm of the cell body. They are seen as fine blue lines running past the nucleus.

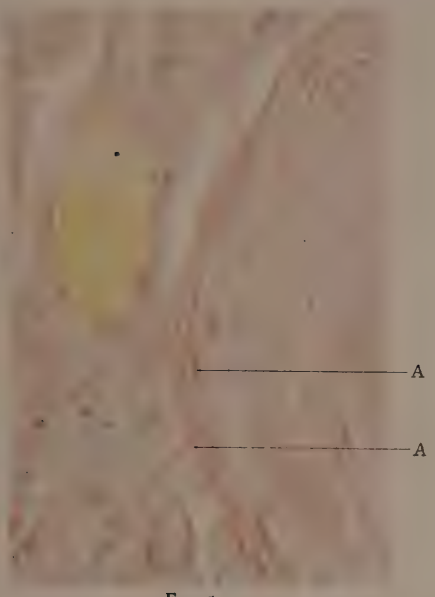

FIG. 5.

Cat. Sciatic. Divided and not sutured. Distal segment (× 300). 5 weeks.
To show a band of new axis-cylinders forming alongside elongated nuclei. They are imbricated and not continuous with each other.
A.A. Band of young axis-cylinders.

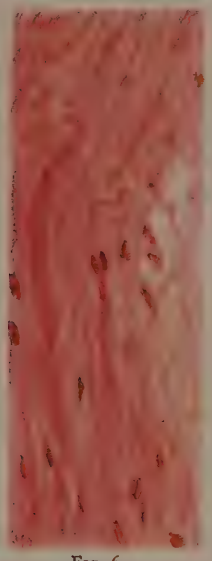

FIG. 6.

Monkey. Musculo-spiral. Divided and not sutured. Distal segment (× 300). 5 weeks.
To show new axis-cylinders.

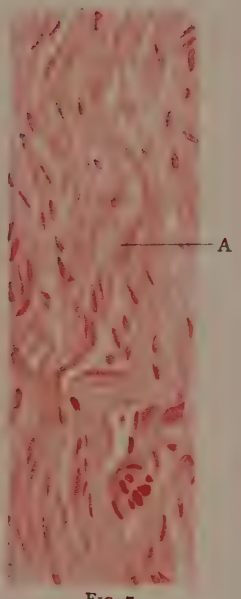

FIG. 7.

Dog. Sciatic. Divided and immediately sutured. 8 weeks. Distal segment (× 300).
To show new axis-cylinders in beaded stage (see A.).

FIG. 8.

Dog. Divided and immediately sutured. Distal segment (× 300). 5 months.
To show new axis-cylinders, each separated by a distinct interval from its corresponding nucleus.

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FIG. 9.

Man. Ulnar nerve. 13 months after division for neuralgia. Distal segment (× 300).
To show regenerated axis-cylinders. Some are beaded. All are smaller than the normal and the neurilemma nuclei are abnormally abundant.

fibres numerous dark elongated nuclei occur in clumps, the long axis of each lying in the long axis of the nerve. (Query, due to interstitial neuritis? The patient had suffered considerable pain.)

At site of division.—There is a well-marked end-bulb, capped by fibrous tissue. In this end-bulb numerous strands of new axis-cylinders are intertwisted and coiled in all directions. The lowest part of fibrous tissue has no nerve fibres in it.

$\frac{1}{2}$ *inch and* $1\frac{1}{2}$ *inches below site of division.* Numerous axis-cylinders are present. Neurilemma nuclei are relatively much more abundant than in a normal nerve. The new axis-cylinders, moreover, are beaded and sinuous in outline (see Plate 14, fig. 9).

COMMENTARY ON THE CHANGES OBSERVED IN THE AXIS-CYLINDERS STAINED BY STROEBE'S METHOD.

A. Degeneration

The changes in the axis-cylinders closely correspond in time to those already described as taking place in the medullary sheaths when stained by the Weigert method. Thus the earliest signs of degeneration appear in the distal segment on the fourth day; they are more marked on the fifth day, the finest axis-cylinders (as in the case of the medullary sheaths) surviving somewhat longer than the larger ones. By the seventh day all the axis-cylinders — fine and coarse alike — have become broken up, although, as stated in Observation 61, in many of the irregular blue-staining masses, formed by the confluent axis-cylinders and myelin sheaths, a portion of axis-cylinder can

occasionally still be recognised. Even at three weeks similar appearances can be detected in the degenerated globules of myelin. After this date, however, the axis-cylinders fade into the surrounding myelin, from which they are no longer distinguishable.

It is particularly to be observed that this process of degeneration of the axis-cylinder — as of the medullary sheath — takes place whether or no the nerve be reunited immediately after its operative division.

B. Regeneration

(1) *In reunited nerve.*

The earliest evidence of this process occurs at the end of two weeks in the lower end of the proximal segment, and is, therefore, in close homology with the regenerative process already observed in the medullary sheaths.

Small colonies of delicate blue threads appear at a considerable distance below the most outlying extremities of the unbroken central axis-cylinders. These colonies are formed independently of the central axis-cylinders, not as outgrowths from them.

In the distal segment, regeneration even in a reunited nerve, is somewhat later in its commencement. At the third week, chiefly at the periphery of the nerve, very fine blue lines are seen forming alongside the proliferated and elongated nuclei of the neurilemma. A comparison of Plate 13, fig. 3, and Plate 14, fig. 4, will show that in the proximal segment the regenerating axis-cylinders are not only earlier in appearance, but also more abundant and greater in substance, inasmuch as those of the proximal segment are clearly visible under a magnification of 300

diameters, while those of the distal segment, a week later, require a magnification of 1000 diameters to demonstrate them with any clearness.

The new axis-cylinders increase steadily in length and in diameter. Their imbricating ends fuse together, and at the end of eight weeks they form long blue beaded lines, whose central ends are continuous with the axis-cylinders of the proximal segment.

At twelve weeks an unstained space has appeared between each new axis-cylinder and the neurilemma nuclei from which it originated. This space, as will readily be understood from the study of the Weigert-stained series, is occupied by the new medullary sheath which clothes the axis-cylinder.

Subsequent changes only serve to render the new axis-cylinders similar in size to those of the central end.

(2) *In the distal segment of a non-united nerve.*

Junction between the proximal and distal segments of a divided nerve is not essential for regeneration of axis-cylinders in the latter. In a specimen of nerve which had not been reunited, the distal segment at the end of four weeks shows young axis-cylinders in their early stage. Figs. 5 and 6, Plate 14, from the monkey and cat respectively, show such regeneration commencing in the manner already described.

But, although new axis-cylinders may thus be laid down in the distal segment of a non-united nerve, they do not attain to full maturity. Their diameter remains less than normal and they are beaded and sinuous (see drawing of non-united nerve after thirteen months, Plate 14, fig. 9).

(3) *Transplantation.*

In the few experiments which we performed, no new axis-cylinders were visible in the graft itself at the end of six and a half weeks. But since, already at the fifth week, the Weigert method demonstrates the undoubted existence of new medullary sheaths in the graft, it is probable that the absence of the axis-cylinders with the Stroebe stain is due to imperfections in the method, which, as we have pointed out, is a very uncertain one in its results.

CHAPTER V

THE CELLULAR ELEMENTS

In the following series of observations the nerves were mostly stained by van Gieson's picro-fuchsin and hæmatoxylin method,—a stain which, in peripheral nerves, is specially valuable for the study of their cellular tissue-elements, viz.—leucocytes, connective-tissue cells, and neurilemma-cells.

Observation 86

Cat. Sciatic. Divided and not sutured.
6 *hours.*

Proximal segment.—The nerve has retracted slightly, and is covered at its free end by a thin cap of perineurium. Slight blood extravasation is also present between the nerve fibres at their lower extremities.

Some diapedesis of leucocytes has occurred around the blood-vessels both of the perineurium and of the endoneurium.

Leucocytes are also present between the nerve fibres near their cut ends, and a few also within the sheaths of Schwann. Here and there in the vicinity of the wound the medullary sheaths are broken up into oblong and globular masses.

Observation 87

Cat. Sciatic. Divided and not sutured.
6 *hours.*

Distal segment.—The distal nerve stump has retracted within its perineurium to a much greater extent than is the case with the proximal stump; the free end of the stump is formed by the adipose tissue of the perineurium.

Marked blood extravasation is present between the nerve fibres, especially along the loose tissue of the endoneurium.

Diapedesis of leucocytes has occurred around the blood-vessels of the perineurium. Leucocytes are also seen in numbers between the nerve fibres, and a few within the sheaths of Schwann. This process of diapedesis is most marked in the vicinity of the wound.

Except for the breaking up of medullary sheaths in the immediate vicinity of the wound, the nerve fibres of the distal segment appear normal.

Observation 88

Cat. Sciatic. Divided and immediately sutured.
6 *hours.*

Silk suture seen *in situ*. There is some blood extravasation into the connective tissue in the neighbourhood of the wound. Diapedesis of leucocytes has occurred immediately around the suture, and also into the connective tissue of the perineurium for some distance above and below the wound, more marked, if anything, on the distal side.

Leucocytes are also present between the nerve fibres and occasionally within their sheaths in the vicinity of the wound.

The nerve fibres are crumpled and the medullary sheaths broken up in the immediate vicinity of the wound. Elsewhere they appear normal in structure, both in proximal and distal segments.

Observation 89

Cat. Sciatic. Divided and immediately sutured.
12 *hours.* (Stained by safranin.)

Similar appearances are seen as in six hours' section. Diapedesis of leucocytes, etc. There is no fragmentation of myelin in the distal segment except in the immediate vicinity of the wound.

Observation 90

Cat. Sciatic. Divided and immediately sutured.
18 *hours.*

Diapedesis of leucocytes is more extensive and involves the whole of the *distal* segment. The *proximal* segment only shows diapedesis in the vicinity of the wound.

In a specimen of the same date, stained with safranin, similar changes are visible. No difference can be detected between the appearances of the nerve fibres in the proximal and distal segments.

Observation 91

Cat. Sciatic. Divided and not sutured.
18 *hours.* (Stained by safranin.)

Proximal segment.—The end of the nerve is capped with

blood-clot, in which are diapedesed leucocytes. Leucocytes are also present in small numbers between the damaged nerve fibres close to the wound. No abnormality of nerve fibres is detected except twisting and breaking up in the vicinity of the wound. The end of the nerve is distinctly "mushroomed."

Observation 92

Cat. Sciatic. Divided and not sutured.

18 *hours.* (Stained by safranin.)

Distal segment.—Most of the nerve-fibres do not differ in appearance from those in the proximal stump, but here and there the axis-cylinders are swollen near their cut ends. The free stump of the nerve is also "mushroomed."

Observation 93

Cat. Sciatic. Divided and not sutured.

24 *hours.* (Stained by safranin.)

Proximal segment.—In the immediate vicinity of the wound the medullary sheaths are reduced to granular débris. The axis-cylinders are less affected, and survive here and there in the midst of the remains of the medullary sheaths.

Observation 94

Cat. Sciatic. Divided and not sutured.

24 *hours.* (Stained by safranin.)

Distal segment. — There is a granular disintegration of the

medullary sheaths in the proximity of the wound. Elsewhere the fibres are not broken down, and do not differ in appearance from the normal.

Observation 95

Cat. Sciatic. Divided and not sutured.
2 *days.*

Proximal segment.—There is diapedesis of leucocytes, extravasation of red corpuscles, and proliferation of connective-tissue cells in the perineurium, and amongst the fibres at the free end. The myelin sheaths are granular near the cut end.

Observation 96

Cat. Sciatic. Divided and not sutured.
2 *days.*

Distal segment. — There is infiltration of nerve sheaths near the free end by red blood corpuscles and by leucocytes. Diapedesis of leucocytes and proliferation of connective-tissue cells are well marked in the perineurium all the way down the section.

The rod-shaped nuclei of the neurilemma have here and there increased in numbers, not diffusely throughout the nerve, but in irregular clusters. The process of division in these cells is obliquely longitudinal, so that the daughter-cells lie in longitudinal series (see Plate 15, figs. 1 and 2).

Observation 97

Cat. Sciatic. Divided and immediately sutured.
2 *days.*

There is diapedesis of leucocytes and proliferation of connective-tissue cells in the neighbourhood of the wound. Both in the *proximal* and *distal* segments there is proliferation of neurilemma cells in irregular clusters (see Plate 15, fig. 2.)

Observation 98

Cat. Sciatic. Divided and not sutured.
3 *days.*

Proximal segment.—At the cut end of the nerve the leucocytes are less numerous than before; their place has been taken by large connective-tissue cells with oval faintly-staining nuclei.

In the vicinity of the wound the nuclei of the neurilemma are much increased in numbers; on tracing the nerve upwards this proliferation of nuclei becomes less and less, until gradually the normal proportion of nuclei is seen.

The proliferated nuclei are shorter and stouter than the normal nuclei of the neurilemma.

Observation 99

Cat. Sciatic. Divided and not sutured.
3 *days.*

Distal segment.—There is proliferation of the neurilemma

nuclei all down the nerve. In specimens stained with safranin the myelin sheaths and axis-cylinders still appear undegenerated.

Observation 100

Cat. Sciatic. Divided and immediately sutured.
3 *days*.

There is a moderate increase in the neurilemma nuclei near the lower end of the *proximal* segment. In the *distal* segment this proliferation of nuclei is more extensive, and occurs with equal intensity all down the nerve.

The myelin sheaths are not broken up in the distal segment. Proliferation of nuclei is best marked in the narrowest neurilemmata which have no myelin within them.

Observation 101

Cat. Sciatic. Divided and immediately sutured in two places half an inch apart. (This is equivalent to transplantation of the intervening half inch.)
3 *days*.

Changes in the *proximal* and *distal* parts of the nerve are as already described for three days' reunion.

The *graft* shows infiltration by leucocytes and connective-tissue cells. The neurilemma nuclei in the graft still stain clearly, but are not undergoing division.

Observation 102

Cat. Sciatic. Divided and not sutured.

4 *days.*

Proximal segment.—The myelin near the free ends of the fibres is broken up into fragments of varying size. There is proliferation of the neurilemma cells near the wound. Many of the invading connective-tissue cells are swollen. They have a wide cell network and a large oval nucleus. They indent the masses of myelin and many of them contain myelin substance within their network (see Plate 15, fig. 3).

Observation 103

Cat. Sciatic. Divided and not sutured.

4 *days.*

Distal segment.—In addition to proliferated connective-tissue cells, there is well-marked proliferation of neurilemma cells. The myelin sheaths are broken up here and there. Most of the sheaths of Schwann still contain myelin in irregular elongated or globular masses. Some of the neurilemma sheaths are filled with large cells so closely packed as to be polygonal. These are proliferated neurilemma cells. Other sheaths which contain myelin show it undergoing indentation by these large cells.

Observation 104

Cat. Sciatic. Divided and immediately sutured.

4 *days.*

There is proliferation of the neurilemma nuclei in the *distal*

segment and in the lowest part of the *proximal* segment. The myelin cylinders are more irregular in outline on the distal than on the proximal side of the wound.

Observation 105

Cat. Sciatic. Divided and not sutured.
5 *days*.

Proximal segment.—There is proliferation of neurilemma cells near the site of the wound, with a local breaking up of myelin into irregular masses. There is no proliferation of nuclei throughout the whole nerve above.

In sections stained with safranin, axis-cylinders can be traced close down to the wound.

Observation 106

Cat. Sciatic. Divided and not sutured.
5 *days*.

Distal segment.—Proliferation of neurilemma cells is well marked all down the nerve, some being oval, some rounded in outline.

The myelin shows signs of fragmentation all down the nerve.

In sections stained with safranin this fragmentation of myelin is very evident. Within many of the myelin masses the broken axis-cylinder may be seen threading its way, often somewhat coiled (see Plate 15, fig. 4).

Observation 107

Cat. Sciatic. Divided and immediately sutured.

5 *days.*

Changes on the *proximal* and *distal* sides of the wound are the same as described for non-united nerve of the same date.

In the scar-tissue around the site of reunion there are numerous leucocytes and proliferated connective-tissue cells.

Observation 108

Cat. Sciatic. Divided and not sutured.

6 *days.*

Proximal segment. — Proliferation of neurilemma cells and fragmentation of myelin are well marked in the vicinity of the wound. The connective-tissue cells in the stump have also proliferated, and the main mass of the stump is broken up into a network formed chiefly by proliferated nuclei, with leucocytes and débris of myelin lying amongst it. Such a mass of broken-up myelin in many cases is seen to have a nucleus in apposition, with, usually, a thin, annular band of protoplasm extending around it from the nucleus.

Observation 109

Cat. Sciatic. Divided and not sutured.

6 *days.*

Distal segment.—Similar changes to those seen on the fifth day are seen, but the proliferation of nuclei is more advanced. The myelin is broken up into fragments within the neurilemmata, and amongst the fragments of myelin there are proliferated neurilemma cells.

Observation 110

Cat. Sciatic. Divided and immediately sutured.

6 *days*.

Similar appearances to five days' reunion are seen, but cell-proliferation is more advanced in the peripheral segment.

Observation 111

Cat. Sciatic. Divided and immediately sutured in two places half an inch apart. (This is equivalent to transplantation of the intervening half inch.)

6 *days*.

In the *graft* there is marked fragmentation of myelin. Amongst the breaking-down myelin there are numerous cells, round and oval. The neurilemma nuclei themselves are not increased in numbers. On the contrary, they are scanty and ill-stained.

Observation 112

Cat. Sciatic. Divided and not sutured.

1 *week*.

Proximal segment.—Towards the lower end of the nerve in the vicinity of the wound nuclei are very abundant, together with numerous polynuclear leucocytes towards the free surface. The broken-up myelin near the lower end is being invaded and absorbed by these cells.

Some of the cell-groups close to the surface at the free end are becoming elongated and spindle-shaped, forming young fibrous tissue.

Observation 113

Monkey. Musculo-spiral. Divided and not sutured.
1 *week.*

Proximal segment. — There is proliferation of cells close to the wound. Infiltration by leucocytes and cellular proliferation are less conspicuous, however, than in the cat.

Observation 114

Cat. Sciatic. Divided and not sutured.
1 *week.*

Distal segment.—There is proliferation of the neurilemma nuclei all down the nerve, and the myelin is broken up into short lengths.

Observation 115

Monkey. Musculo-spiral. Divided and not sutured.
1 *week.*

Distal segment.—Similar changes are seen, less conspicuous than in the cat, so far as cell proliferation is concerned. The myelin is completely fragmented.

Observation 116

Cat. Sciatic. Divided and immediately sutured.
1 *week.*

There is proliferation of the neurilemma nuclei towards the lower part of the *proximal* segment and more markedly in the

entire length of the *distal* segment. There is infiltration of leucocytes and proliferation of connective-tissue cells in the scar-tissue and in its vicinity.

The myelin is irregularly broken up in the distal segment, and in the proximal segment in the vicinity of the wound.

Observation 117

Monkey. Musculo-spiral. One month after excision of a portion of the nerve, 25 mm. of sciatic nerve from a freshly killed rabbit was sutured into the gap.

2 *weeks later* the specimen was obtained.

Only the proximal segment and a small piece of the upper end of the graft were seen in this section.

The *graft* shows breaking up of myelin into globules and proliferation of connective-tissue cells in apposition to myelin masses.

Observation 118

Cat. Sciatic. Divided and not sutured.

2 *weeks.*

Proximal segment.—There are large numbers of proliferated cells, chiefly towards the free end of the nerve; of these the elongated neurilemma nuclei lie along the margins of the fibres, whilst the rounded connective-tissue nuclei lie between the elongated ones or amongst the breaking-down myelin.

The stump of the nerve is formed by a vortex of elongated nuclei interspersed with rounded or oval nuclei and broken-down myelin. The whole is covered by a cap of perineurium with numerous fat cells.

Observation 119

Cat. Sciatic. Divided and not sutured.
2 weeks.

Distal segment.—There is proliferation of cells, chiefly of the rounded or ovoid variety, amongst the myelin fragments. Compared with the distal segment of a reunited nerve of the same date, the long rod-shaped neurilemma nuclei are relatively less numerous.

Observation 120

Cat. Sciatic. Divided and immediately sutured.
2 weeks.

There is an enormous proliferation of cells all down the peripheral segment and at the lower part of the proximal segment. The myelin in the peripheral segment is completely fragmented.

The cells are seen to be of two varieties :—

A. Neurilemma cells, with elongated rod-shaped nuclei, three or four times as long as they are broad. They lie with their long axes in the line of the nerve, and apparently in close apposition to the neurilemma.

B. Connective-tissue cells, with round or short oval nuclei. They lie either amongst the masses of myelin or between the columns of elongated nuclei (see Plate 15, fig. 5).

In the intermediate scar-tissue the cells with elongated and those with rounded nuclei are mixed in haphazard fashion, with leucocytes scantily interspersed.

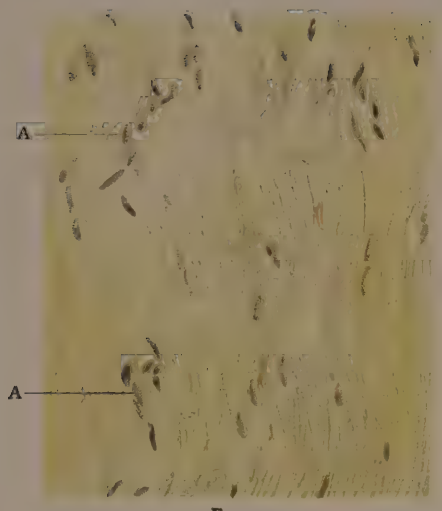

FIG. 1.

Cat. Sciatic. Divided and not sutured. Distal segment (× 300). 2 days.
To show early stage of proliferation of neurilemma cells.
A.A. Groups of proliferating cells.

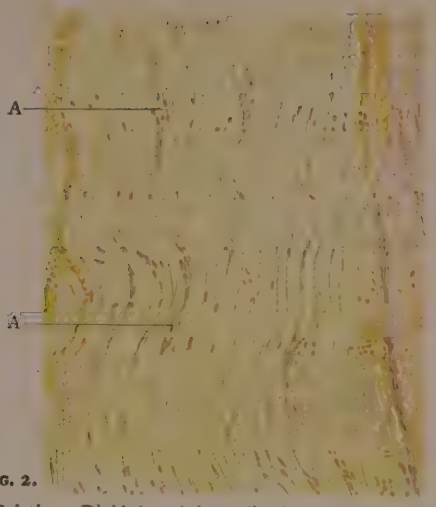

FIG. 2.

Cat. Sciatic. Divided and immediately sutured. Distal segment (× 100). 2 days.
To show early stage of proliferation of neurilemma cells.
A.A. Groups of proliferated cells.

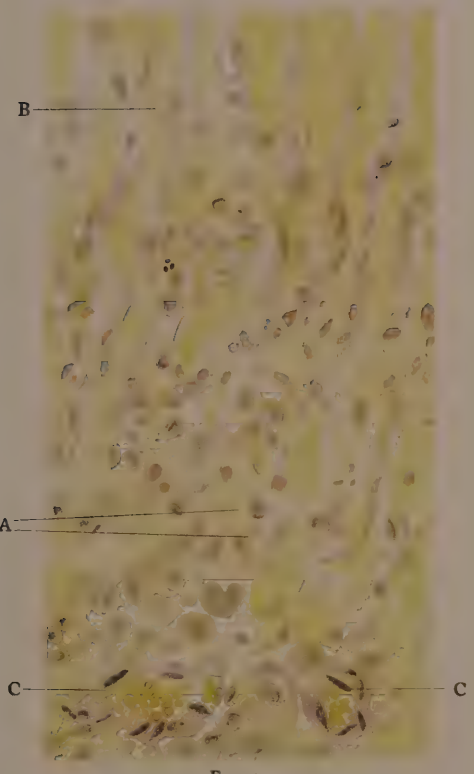

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FIG. 3.

Cat. Sciatic. Divided and not sutured. Proximal segment (× 300). 4 days.
To show invading and multiplying connective-tissue cells, many of which are feeding on the disintegrating myelin.
A.A. Connective-tissue cells distended with myelin.
B. Myelin indented by a connective-tissue cell.
C.C. Capillaries.

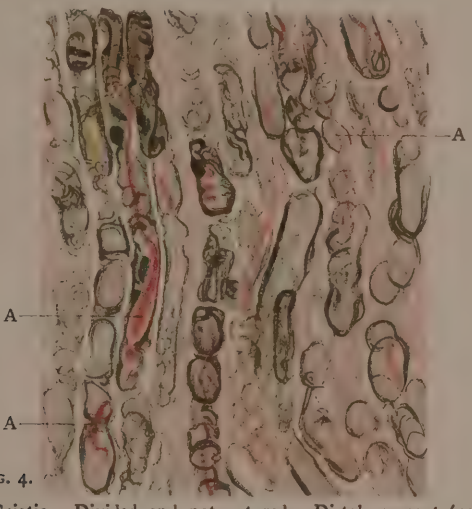

FIG. 4.

Cat. Sciatic. Divided and not sutured. Distal segment (× 300). Stained by safranin. 5 days.
To show breaking up of myelin and of axis-cylinders.
A.A.A. Axis-cylinders.

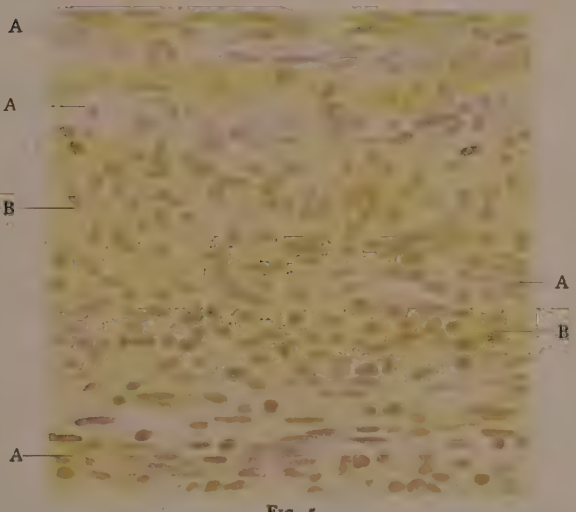

FIG. 5.

Cat. Sciatic. Divided and immediately sutured. Distal side of reunion (× 300). 2 weeks.
To show columns of neurilemma cells separated by masses of connective-tissue cells; many of the latter containing myelin.
A.A.A.A. Columns of neurilemma cells.
B.B. Connective-tissue cells.

Observation 121

Dog. Sciatic. Divided and not sutured.
3 *weeks.*

Proximal segment. — There is proliferation of nuclei at the lower end of the nerve. The stump is seen to be formed by a vortex of elongated and rounded nuclei, chiefly the latter, embedded in a delicate stroma and with numerous young capillaries full of blood. A few rounded masses of myelin are scattered here and there amongst this nucleated connective tissue towards its central end.

Observation 122

Cat. Sciatic. Divided and not sutured. Fibrous junction occurred.
3 *weeks.*

The *distal* segment shows longitudinal rows of elongated nuclei. Between these rows are short oval or rounded cells and masses of myelin. Most of the globules of myelin have a rounded nucleus in apposition to them.

The *intermediate scar-tissue* shows numerous rounded connective-tissue cells much more loosely packed than those of the nerve sheath.

The *proximal* segment shows proliferation of elongated neurilemma cells, and of rounded connective-tissue cells as already described.

Observation 123

Cat. Divided and immediately sutured.
3 *weeks*.

Towards the lower end of the *proximal* stump the elongated neurilemma cells form longitudinal rows. Amongst them are a few rounded nuclei and broken-up myelin globules, irregularly interspersed.

In the *intermediate tissue* an irregular vortex of elongated nuclei is seen, in whose interstices rounded nuclei occur.

In the *peripheral* segment the long neurilemma nuclei are again arranged in parallel rows, but the individual nuclei of each chain are not so close together as in the lower end of the proximal stump or in the intermediate tissue. Moreover, the protoplasm of these cells is visibly spread out, forming long processes between the nuclei. Broken-down myelin in globules and numerous rounded nuclei lie between these rows.

Observation 124

Dog. Sciatic. Divided and not sutured.
4 *weeks*.

Proximal segment.—The appearances are similar to those in the three weeks' specimen, viz. a cap of young connective tissue with proliferated nuclei, capillaries, etc.

Observation 125

Dog. Sciatic. Divided and not sutured.

4 *weeks*.

Distal segment.—The upper end is formed by a vortex of cells with elongated and rounded nuclei. In the main trunk of the nerve below, the rows of longitudinal nuclei are still distinct, and there is a longitudinal fibrillation of the stroma in which they lie.

Broken-down rounded masses of myelin are seen here and there, less numerous than at three weeks and staining more faintly, most of them in apposition to rounded or short oval nuclei which lie against their surface.

The longitudinal elongated nuclei now outnumber the rounded or oval ones.

Observation 126

Cat. Sciatic. Divided and immediately sutured in two places half an inch apart, which is equivalent to transplantation of the intervening portion.

4 *weeks*.

The *proximal* end terminates in an irregular interlacing mass of cells. The *distal* end emerges from a similar vortex of nuclei. The appearances of these are the same as in a non-united nerve of the same date.

The *graft* consists mainly of cells, chiefly of the rounded or oval variety, with a number of rod-shaped ones interspersed, but their arrangement is irregular and not in the definite parallel rows seen in the distal end.

Observation 127

Monkey. Musculo-spiral. 30 days. Divided and not sutured. Fibrous junction occurred.

At the *proximal* end of the specimen, where the nerve enters the scar-tissue, degenerated masses of myelin, faintly stained, are seen in apposition to rounded or oval nuclei.

The elongated nuclei form long rows running sinuously in various directions, and each of these nuclei when cut longitudinally has a fine hair-like process of protoplasm tailing off from both poles.

In the *distal* end a similar process is going on in the elongated nuclei amongst the masses of myelin and of rounded nuclei (see Plate 16, fig. 6).

Observation 128

Cat. Sciatic. Divided and not sutured. Fibrous junction occurred.

5 *weeks*.

The *proximal* end terminates as usual in a vortex of spindle-shaped neurilemma nuclei, with rounded connective-tissue nuclei between.

The *intermediate tissue* between the proximal and distal ends is formed of loose connective tissue with numerous young capillaries.

The *peripheral* segment is very cellular. It is made up of longitudinal rows of neurilemma nuclei with rounded connective-tissue cells and masses of myelin in the interstices (see Plate 16, fig. 7).

Observation 129

Dog. Sciatic. Portion excised. Fibrous junction occurred.
5 *weeks.*

The *proximal* segment has become accidentally twisted, so that many of its fibres are cut in transverse section near their lower end. Their appearance in such a field is seen in Plate 16, fig. 8. Here and there within the old neurilemma, numerous nuclei are grouped amongst bundles of newly-formed nerve fibres.

In the *distal* segment the cells are chiefly the longitudinal neurilemma ones, arranged in parallel series. Rounded connective-tissue nuclei are scantily scattered among them.

Observation 130

Monkey. Musculo-spiral. Divided and not sutured. Fibrous junction occurred.
5 *weeks.*

The appearances are similar to those already described for non-united nerve of the same date in the cat.

Observation 131

Monkey. Median nerve exposed and 1 centimetre excised. Three weeks later, 8 millimetres of a sheep's nerve were inserted into the gap. Five weeks later again, the monkey was killed.

The *proximal* segment shows proliferation of neurilemma cells at its lower extremity as usual. The *graft* is made up

of a mass of elongated neurilemma cells with closely-packed rounded connective-tissue cells between them.

Here and there in the graft there are ribbons of cells arranged in longitudinal series with elongated nuclei. The protoplasm of adjacent cells is spun out, so that they sometimes coalesce.

The peripheral segment is not cut in this section.

Observation 132

Same specimen as in Observation 131, two inches below the level of the graft.

The *distal* segment is made up of sinuous rows of elongated granular nuclei from whose extremities deeply-staining threads project, so as to form continuous wavy lines. The elongated nuclei are applied to the sides of these lines, and are here and there undergoing division (see Plate 16, fig. 9).

No rounded nuclei of the ordinary connective-tissue type occur between the rows of elongated ones.

Observation 133

Dog. Sciatic. Portion excised. A fortnight later, $4\frac{1}{2}$ centimetres of a cat's sciatic were sutured into the gap, after rawing the upper and lower segments. *Six and a half weeks* later the dog was killed.

Junction of proximal segment with graft.—The lower part of the proximal segment shows proliferation of neurilemma cells as already described.

In the graft itself the cells at the upper end are cut in various

directions. Lower down they are seen in longitudinal section. Cell-proliferation is very marked; the rod-like and the oval nuclei are fairly closely packed together. Traces of old myelin are but scanty.

In middle third of graft.—There is moderate proliferation of rod-shaped and more markedly of oval cells. In addition, there is well-marked infiltration of polynuclear leucocytes between the proliferated nuclei.

Below graft.—Sections at levels $2\frac{1}{2}$, $4\frac{1}{2}$, and $6\frac{1}{2}$ inches below the graft show remnants of myelin irregularly distributed, between sinuous rows of elongated coarsely-granular nuclei. Rounded or irregularly oval nuclei are occasionally found in close apposition to the myelin masses.

The elongated nuclei form chains, closely set, end to end. With an oil-immersion lens fine protoplasmic processes can be seen growing out from the ends of certain of the elongated nuclei.

Observation 134

Dog. Sciatic. Divided and immediately sutured.
8 *weeks*.

The lower part of the *proximal* segment shows the usual proliferation of rod-shaped neurilemma nuclei with shorter, oval, connective-tissue nuclei interspersed.

The silk suture is seen *in situ* surrounded by oval connective-tissue cells. In the region of the junction the arrangement of elongated nuclei is very irregular. On tracing the section down towards the *distal* segment of the nerve below, the arrangement of

nuclei again becomes more regular, longitudinal nuclei running in parallel sinuous rows with a moderate number of short oval nuclei interspersed between them.

The longitudinal nuclei are closely set, end to end.

Numerous fine threads of a pink colour are seen running longitudinally amongst the chains of nuclei. These are threads of fibrous tissue.

Only very scanty globules of myelin are discoverable amongst the rows of nuclei.

Observation 135

Dog. Sciatic. Divided and immediately sutured.
12 *weeks.*

The *distal* segment shows rows of elongated nuclei, regularly arranged.

These are in apposition to sinuous columns of yellow stained material :—young myelin (see Plate 16, fig. 10).

Observation 136

Dog. Sciatic. Divided and immediately sutured.
16 *weeks.*

The appearances are exactly similar to those seen at twelve weeks. The myelin in the distal segment forms sinuous columns between the rows of nuclei.

Observation 137

Human ulnar nerve. *Four months* after accidental division. Fibrous junction occurred.

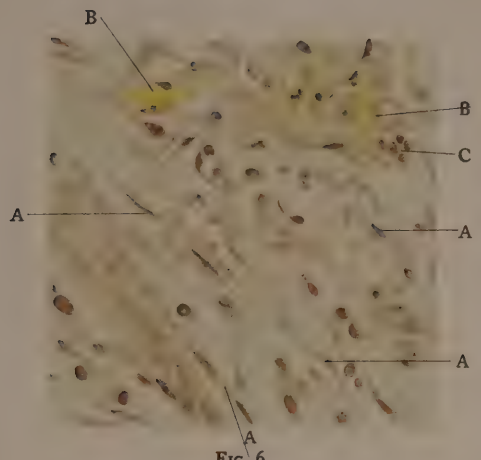

FIG. 6.

Monkey. Musculo-spiral. Divided and not sutured. Fibrous junction occurred. Distal segment (× 300). 30 days.
To show fine protoplasmic processes stretching out from the opposite poles of the neurilemma nuclei.
A.A.A.A. Neurilemma cells with protoplasmic processes.
B.B. Cells devouring myelin.
C. Cluster of proliferating connective-tissue cells.

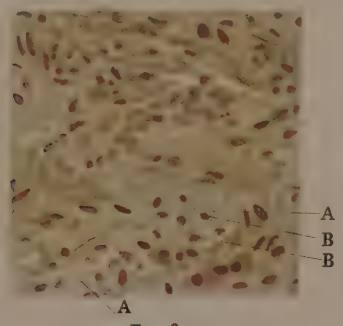

FIG. 8.

Dog. Sciatic. Portion excised. Fibrous junction occurred. Proximal segment (× 300). 5 weeks.
To show newly formed nerve-fibres within an old neurilemma.
A. New fibres, each with an axis-cylinder, the latter appearing as a dot on transverse section.
B.B. Rod-shaped neurilemma nuclei appearing circular on transverse section.

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FIG. 10.

Dog. Sciatic. Divided and immediately sutured. Distal segment (× 300). 12 weeks.
The yellow material between the columns of nuclei is myelin.

FIG. 7.

Cat. Sciatic. Divided and not sutured. Fibrous junction occurred. Distal segment (× 100). 5 weeks.
To show enormous proliferation of neurilemma cells—compare Fig. 2 of Plate 15. The elongated neurilemma nuclei are arranged longitudinally and in columns. Between them are the rounded nuclei of the connective-tissue cells.

FIG. 9.

Monkey. Median. 5 weeks after grafting of a portion of sheep's sciatic nerve. Distal segment, below graft (× 300).
To show the neurilemma nuclei with long processes tending to form chains. No old myelin fragments and no connective-tissue cells.

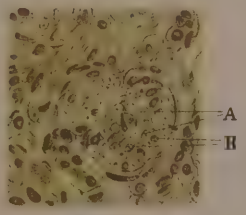

FIG. 11.

Man. Ulnar. 4 months after accidental division (× 300). Lower part of proximal segment. To show formation of numerous new nerve-fibres, complete with axis-cylinders, within a single neurilemma sheath.
A.A. Nerve-fibres in transverse section.
B.B. Proliferated neurilemma nuclei.

The *proximal* segment shows a well-marked bulb, in which are closely set columns of elongated neurilemma nuclei, interlacing in various directions.

Here and there an old neurilemma sheath cut in transverse section is seen to contain numerous young medullary sheaths, each with an axis-cylinder in the centre, together with a number of proliferated nuclei (see Plate 16, fig. 11).

In the *distal* segment closely packed rows of elongated nuclei are seen. Between these here and there are longitudinal yellow stained lines of myelin, much narrower than in a reunited nerve of the same date.

Observation 138

Monkey. Median. Divided and not sutured. Fibrous junction occurred.

5 *months.*

In the *distal* segment the longitudinal rows of nuclei are very closely packed. A few scanty myelin columns can be made out, and here and there fine processes project from the opposite poles of an elongated nucleus, forming longitudinal chains.

A pad of muscle separates the proximal from the distal segment.

On the *proximal* side of this pad a well-marked bulb exists, formed chiefly by interlacing rows of neurilemma cells. These nuclei show similar threads growing out from each end as in the distal segment.

Observation 139

Dog. Sciatic. Divided and immediately sutured.

5 *months.*

The changes in the *proximal* segment are similar to those already described in Observation 138.

The *distal* segment shows new myelin sheaths both in longitudinal and in transverse section.

Observation 140

Human ulnar. *Thirteen months* after division. Fibrous junction occurred.

In sections above the level of the original division, the nerve appears normal, so far as its fibres are concerned, but interstitial connective tissue is in excess, as if from interstitial neuritis (possibly associated with the neuralgia for which the nerve was originally divided).

At site of division.—There is a large end-bulb at the lower end of the proximal segment, formed as usual of interlacing neurilemma nuclei.

The *peripheral* part of the nerve below shows longitudinal rows of neurilemma nuclei. No signs (with this stain) of new myelin are found.

In sections $\frac{1}{2}$*-inch and* $1\frac{1}{2}$*-inch below level of division.*—No myelin is seen with this stain. The nerve consists of closely packed rows of nuclei.

COMMENTARY ON THE CELLULAR CHANGES OBSERVED IN SECTIONS STAINED BY VAN GIESON'S METHOD.

A. Leucocytes

Specimens obtained six hours after the injury exhibit merely the effects of a recent traumatism, namely extravasation of blood and diapedesis of leucocytes, such as would occur in any injured tissue. At the end of eighteen hours, as described by one of us in a former paper (31), the leucocytic invasion reaches its maximum. It is particularly to be noted that the whole extent of the distal segment is invaded whilst the proximal segment is only so affected in the vicinity of the wound. It is therefore evident that as a consequence of loss of function, some chemical alteration has already occurred in the distal segment, sufficient to induce the leucocytes to wander into the dying tissue, and this in spite of the fact that no structural changes are detected either in the axis-cylinders or medullary sheaths until the fourth day.

The function of the leucocytes is apparently a transient one, for at the end of three days many of them have been already replaced by migratory connective-tissue cells. From this time onwards leucocytes become less and less numerous, until at the end of two weeks they are no longer in excess.

B. Connective-tissue Cells

The microscopic appearance of these cells when free differs entirely from that of the leucocytes. The nucleus of each con-

nective-tissue cell is large, oval, vesicular, and stains faintly. It is therefore totally unlike that of the common variety of migratory leucocyte which has a multipartite, deeply-staining nucleus.

The proliferation of connective-tissue cells, from whatever source derived (whether from the connective-tissue elements of the nerve-trunk, or from the surrounding structures) begins at a distinctly later period than the leucocytic invasion. A possible explanation may be offered in the fact that leucocytes, being already present in large numbers in the blood, form a standing army ready to move instantly in the direction of an irritant, whereas the connective-tissue cells must abandon their quiescent habit and proceed to multiply, or mobilise, before they can advance into a tissue, which it is their function to absorb and replace.

At the end of two days the invading connective-tissue cells are present in considerable numbers, both in the fibrous perineurium, and to a less extent between the nerve fibres. This cellular proliferation, as in the case of the leucocytes, is found all the way down the distal segment, whether it has been reunited or not, whilst in the proximal segment it is confined to the vicinity of the wound.

At the end of three days the connective-tissue cells are still more numerous, and on the fourth day they are in a position to assault the myelin. They indent it and take it into their substance. In this work, namely the absorption of myelin, they are aided to some extent, as will be later described, by the proliferated neurilemma cells. The process of absorption continues until there is no longer any old myelin left to be absorbed. At the end of five weeks, in the distal segment of a non-united nerve, only small fragments of myelin can be found, and from this date onwards the connective-tissue cells are more and more outnumbered by the

neurilemma cells. Those connective-tissue cells that remain, as food becomes scanty, fulfil their determinate hereditary tendency, and resume their original resting stage as constituents of fibrous tissue.

C. Neurilemma Cells

The appearance of the nucleus of a proliferating neurilemma cell differs from that of the connective-tissue cell as well as from that of the leucocyte, from both of which it can be readily distinguished. It is rod-shaped, and its long axis lies parallel with that of the nerve-fibre. It absorbs nuclear stains with the same intensity as the connective-tissue nucleus ; but even when both varieties of cells are in great abundance (see Plate 16, fig. 7) there is no difficulty in distinguishing the long rod-shaped nuclei of the one from the short oval nuclei of the other. It is not proposed to discuss in this research the embryological origin, whether mesoblastic or epiblastic, of the neurilemma cell, and in differentiating the neurilemma cell from the ordinary connective-tissue cell we do not express any opinion as to its embryological source.

The earliest indication of proliferation occurs in the distal segment of a divided nerve at the end of two days. By this time, probably in response to some early chemical change in certain of the medullary sheaths with which they are in contact, the neurilemma cells abandon their resting condition, and commence actively to multiply in discrete patches. Each parent-cell divides in an obliquely longitudinal plane, so that the resulting daughter-cells somewhat overlap each other, and by successive divisions they form closely set longitudinal columns or chains (see Plate 15, figs. 1 and 2).

Putting aside for the moment the leucocytic invasion already discussed, the earliest cells observed to multiply in the degenerating distal segment of a divided nerve are not the cells of the ordinary connective tissue, but those of the neurilemma. This is what might be expected, since the neurilemma cells are in close apposition with the medullary sheaths, whose constitution is a fatty one in which chemical changes rapidly ensue when function ceases. The connective-tissue cells, on the other hand, not being in such intimate relation to the medullary sheaths, receive the chemical stimulus which induces proliferation at a distinctly later period.

The proliferation of the neurilemma cells, at first patchy, soon becomes general. It has commenced at the lower end of the proximal segment by the end of the third day, but it does not extend in a central direction beyond the vicinity of the traumatism, whereas in the distal segment it takes place simultaneously, at this date, throughout the whole length of the nerve, whether it has been sutured or not. This proliferation of the neurilemma cells has for its immediate object the removal of the functionless fatty *débris* of medullary sheaths and axis-cylinders, in which work the neurilemma cells co-operate with the connective-tissue cells which come in, as already described, from the perineurium. The work of fat absorption, however, though initiated by the neurilemma cells, is performed mainly by the migrated connective-tissue cells, and even while this process is as yet unfinished the neurilemma cells give up the struggle for the remaining spoil of food, and resign themselves to the formation of separate and compact columns, the individual elongated cells of which are arranged longitudinally (see Plate 15, fig 5—two weeks). The elongated cells which form these columns proceed

later to send out from their opposite poles fine protoplasmic processes, which gradually increase in length. This appearance is distinct at four weeks (see Plate 16, fig. 6), and still more marked at the end of five weeks (see Plate 16, fig. 9). The process is essentially the same whether the distal segment remains ununited or has been sutured to the proximal.

The further development of the neurilemma cell towards the formation of a perfect fibre is seen in Plate 16, fig. 10 (twelve weeks), in which the nuclei are apposed to threads of newly formed myelin (compare Plate 4, fig. 14 of the Weigert series).

Finally it is to be observed that an old neurilemma sheath is not replaced by one set but by several sets of new sheaths, each of which corresponds to a newly formed axis-cylinder (see Plate 16, fig. 11). As the neurilemma cell of the old sheath multiplies, its place is taken by a new and numerous generation of cells, each of which is potentially capable of forming a segment of a complete nerve fibre. The more the specimens are studied the more is the conclusion forced upon the mind of the observer that for the regeneration of a peripheral nerve fibre (not only the axis-cylinder, but also the medullary and neurilemma sheaths) the activity of one variety of cell, and one variety only is responsible. That cell is the neurilemma cell.

The cellular changes in transplanted nerve

The number of experiments with transplanted nerves, although not large, is sufficient to demonstrate clearly the fundamental fact that the cells, and indeed the whole structure, of the graft, play no active part in regeneration beyond that of affording a particularly

suitable scaffolding for the building of new nerve tissue between the proximal and distal segments. The graft, in fact, like blood-clot, is entirely absorbed and replaced by new tissue. It would appear that it is particularly well adapted for a scaffolding, since its original structure may be compared to a bundle of tubules through which, or between their interstices, the incoming cells may readily advance and finally be predisposed to assume a longitudinal direction. This the elements of the graft originally possessed, and it would seem to be an important factor in securing a successful result. At a date (three days) when in the distal segment of the divided nerve the neurilemma cells have already begun to proliferate, no such vital reaction is seen in the cells of the graft. More than this, at the end of six days, when the proliferation of neurilemma cells of the distal segment is well advanced, those of the graft are scanty in numbers and take the nuclear stain badly—a sure indication of a lethal change. The fragmentation of myelin being a destructive and not a constructive process, goes on in the graft as usual, and is seen to be associated with a great invasion of the graft by the food-seeking connective-tissue cells.

At the end of four weeks, in the place of the graft there has been substituted a tissue which is now almost wholly cellular. The cells are almost all of the connective-tissue type, with short oval nuclei, but amongst them well-stained, rod-shaped nuclei can be clearly distinguished. These rod-shaped nuclei rapidly increase in numbers, and by the end of five weeks they have arranged themselves into longitudinal ribbons or columns for the purpose of forming nerve fibres to connect the upper and lower segments. Between the columns are masses of connective-tissue cells without any regularity of arrangement. Under a high power each

neurilemma cell in these columns is seen to extend long thread-like processes in both directions, upwards and downwards, and the threads of those cells which are in longitudinal series coalesce. It may be recalled that at this date numerous myelin sheaths can be demonstrated by the Weigert method in the graft.

In a specimen obtained at the end of six and a half weeks, in which a considerable length of nerve ($4\frac{1}{2}$ cm.) was transplanted from the cat to the dog, it is instructive to note that while the ends of the graft are well supplied with rod-shaped nuclei, which have voyaged into them from the proximal and distal segments of the living nerve, yet in the centre of the graft their numbers are smaller, and interspersed amongst them are numerous connective-tissue cells and also leucocytes, the latter being an indication that the replacement of the central segment of the graft by living tissue is less advanced than that of any other portion.

CHAPTER VI

GENERAL CONCLUSIONS

A COMPARATIVELY brief reference is all that we shall here make to the enormous mass of literature which has accumulated on the subject of the regeneration of peripheral nerves. For further accounts the reader is referred to the excellent bibliographies appended to the papers of Galeotti and Levi (8) and of Kennedy (16).

The fact has long been admitted that healing is possible in a divided nerve after its proximal and distal segments have been brought together, either by direct apposition or by the interposition of a graft of nerve substance. But there is a wide diversity of opinion as to the exact manner in which this regeneration is accomplished. Broadly speaking, previous workers at the subject may be classified into two schools, which we may term the "central" and the "peripheral" respectively.

The overwhelming majority of writers belongs to the "central" school, according to which it is maintained that the new axis cylinders which appear in the regenerated distal segment are direct outgrowths from those in the central segment, the young axis-cylinders sprouting downwards, and worming their way into the empty neurilemma sheaths of the distal segment, and replacing the old axis-cylinders, which had previously become degenerated and

been absorbed. According to this doctrine, the peripheral segment of a divided nerve plays an entirely passive *rôle*, and merely undergoes "neurotisation" (to use Vanlair's expression), and no regeneration can take place in the distal segment unless it has been united to the proximal.

Such is the classic view of the elder Waller (39) which, amplified by Ranvier (27), and fortified by the embryological researches of His (13), Kölliker (17), and others, was for a time universally accepted. And in more recent years other workers (amongst whom may be mentioned Howell and Huber (14), von Notthafft (23), Stroebe (33), Vanlair (37), Gürwitsch (9), Kolster (18), Harrison (11)), employing more delicate staining methods, have also supported this theory, modifying it only in so far as that whilst they still regard the axis-cylinders as outgrowths from the proximal segment, the neurilemmata are admitted to be derived from elements in the distal segment. Some hold with Ranvier and Vignal (28) that the new medullary sheath is secreted by the ensheathing neurilemma cells, whilst Gürwitsch, Kolster, and others maintain that the myelin sheath in its origin has nothing to do with the neurilemma, but arises as a product of metabolism of the axis-cylinders.

The "peripheral" theory, on the other hand, is that according to which the new fibres in the distal segment—axis-cylinders, medullary sheaths and neurilemmata alike—are formed from pre-existing cells in the distal segment itself. The young axis-cylinders and medullary sheaths are laid down in the first instance in the distal segment, and they become attached later to those of the central segment, thereby restoring the conductivity of the nerve-trunk.

To this view we unhesitatingly declare our adherence, our results being an amplification of those obtained by Tizzoni (35), Cattani (5), von Büngner (4), Kennedy (16), and Bethe (2), in divided nerves, and by the developmental researches of Beard (1), Engelmann (6), and Galeotti and Levi (8).

THE PROCESS OF DEGENERATION

When a nerve-trunk is divided, its peripheral segment undergoes degeneration, and it does so whether or not it is brought into apposition with the proximal segment by sutures, either immediately after division, or at a later date. The degenerative changes also affect a small portion of the proximal segment in the vicinity of the wound.

(*a*) *Cellular changes*

The earliest changes that can be observed microscopically in a divided nerve are those occurring in its cellular elements. Within six hours after the initial blood-extravasation, due to the original traumatism, diapedesis of leucocytes occurs and rapidly (by the 18th hour) reaches its maximum. This leucocytic invasion affects the whole of the distal segment of the nerve, whilst the proximal segment is only affected in the neighbourhood of the wound. After three days, connective-tissue cells wandering in, begin to take the place of the leucocytes. The leucocytes then progressively diminish in numbers, and after two weeks they are no longer in excess, having by that time been replaced by proliferated connective-tissue cells.

The connective-tissue cells begin to proliferate during the second day after the trauma, and they also, as in the case of their

predecessors, the leucocytes, invade the whole of the distal segment of the nerve-trunk, whilst the proximal segment is only so affected in the neighbourhood of the wound. On the fourth day, the connective-tissue cells commence to indent the fatty substance of the myelin sheaths and to take it into their substance, and this process of myelin absorption continues until the whole of the myelin—and with it the degenerated axis-cylinder within—is completely absorbed. No definite date can be determined by which the process of absorption is complete. The greater part of the myelin, however, is removed by the end of five weeks, scanty remnants being all that can be detected from that date onwards. As the supply of fatty material in the degenerating medullary sheaths and axis-cylinders diminishes, the connective-tissue cells become less numerous, and are at length outnumbered by the gradual increase of neurilemma cells. Those connective-tissue cells which still remain, after absorbing the last remnants of fatty *débris*, ultimately become spindle-shaped, and proceed to form fibrous tissue between the chains of neurilemma cells. The degenerated nerve-trunk therefore becomes hard, fibrous, and cirrhosed.

The neurilemma cells commence to proliferate on the second day after the injury, but in an irregular, patchy fashion. At the outset, their proliferation is more energetic than that of the connective-tissue cells, and during this early stage the neurilemma cells have an absorptive action on the degenerating medullary sheaths. But soon, as the connective-tissue cells increase in numbers, the neurilemma cells cease to attack the myelin; they leave that function to the connective-tissue cells, and continue to proliferate in columns. The young neurilemma cells preserve the original longitudinal direction of their parent cells, and from their

opposite poles they shoot out fine protoplasmic processes which gradually increase in length.

(*b*) *Changes in the axis-cylinders and medullary sheaths*

No obvious histological changes occur in the axis-cylinders or medullary sheaths until the fourth day (in the cat). On that date, however, fragmentation, both of the axons and of the fatty sheaths, commences, probably the sequel of a preceding chemical or molecular alteration which, though invisible by the microscope, is evidenced by the cellular proliferation already referred to. The fragmentation process rapidly increases in intensity. An interesting point in this connection, and one to which, so far as we are aware, attention has not hitherto been directed, is that the smallest nerve fibres possess a greater vitality or power of resistance than the coarser ones. Thus, on the fifth day, when fragmentation is well established in the coarser axons and myelin sheaths, the fine fibres are still unbroken. Their survival, however, is but short-lived, for by the seventh day they too, like their coarser neighbours, have succumbed to the disintegrating process. We are unable to agree with Fleming's (7) statement that in the process of degeneration the finest fibres exhibit more advanced degeneration than those of ordinary size.

The fragmented axis-cylinders, which at first could be distinguished within the short, broken-up lengths of myelin, soon lose their individuality ; they no longer respond to special stains but undergo a katabolic process whereby they become merged into the fragmented myelin, forming homogeneous, diffusely-staining, globular masses. These fatty remains of axis-cyclinders and

medullary sheaths are gradually entirely removed by the action, chiefly, of the connective-tissue cells which have proliferated and migrated in for that purpose. The neurilemma cells play but a transient *rôle* in the absorption of fatty *débris;* they have other functions to perform, namely, to attempt regeneration of axis-cylinders and medullary sheaths.

The degenerative process in the proximal segment takes place only at its lowest pole, near the wound. In the distal segment it occurs throughout the entire extent. The rapidity of the process is in no way affected by the suturing or otherwise of the distal to the proximal segment.

THE PROCESS OF REGENERATION

The changes which characterise regeneration of a divided nerve differ according to whether or not the proximal and distal segments have been brought into apposition. But the difference in the two cases is one merely of degree and not of kind. Even in the distal segment of a non-united nerve regeneration of axis-cylinders and of medullary sheaths takes place, although full maturity of the new nerve-fibres is not attained unless the distal segment be joined to the proximal, so that their fibres may become functionally continuous.

(*a*) *Regeneration in the proximal segment of a divided nerve*

These changes produce the appearance of the so-called "end-bulb," in which the fountain-like arrangement of new fibres gives a characteristic appearance which has misled the majority of observers to the conclusion that the new nerve-fibres have grown out from the central axons, and that, finding it impossible to grow downwards any farther, they then turn back on themselves in a futile

manner, thus forming the end-bulb. Such a conclusion is, however, erroneous. Our observations clearly demonstrate the fact that, even after an interval no longer than twenty-four hours, a structure, which we have called the "primitive end-bulb," is already present, which has been produced by the curling up of the loose ends of the divided fibres. Subsequently, a deposition of new axis-cylinders and of medullary sheaths takes place in this primitive end-bulb, which acts merely as a scaffold on which the permanent end-bulb is deposited. And the deposition of new fibres in the end-bulb is accomplished, as would be expected, by precisely the same process as that by which regeneration of the distal segment is attained, namely, by the action of the neurilemma cells which, taking on an active neuroblastic function, secrete short lengths of axis-cylinders and of medullary sheaths. And these, linking themselves together into chains, form continuous axis-cylinders and medullary sheaths.

(*b*) *Regenerative process in the distal segment of a divided nerve, after suturing of distal to proximal segment*

The earliest signs of regeneration in the distal segment occur at the end of three weeks. At this date, in specimens impregnated by the Golgi method, numerous longitudinal "spider-cells" can be seen, shooting out young, beaded axis-cylinders from their opposite poles. In the intermediate scar-tissue between the proximal and distal segments, similar spider-like neuroblasts are also visible, whose processes interlace irregularly, and form a network of new axis-cylinders. The new axons, comparatively short at three weeks, rapidly increase in length, and at the end of four weeks have grown so as to overlap and anastomose.

Corroborative evidence of this process is afforded by the Weigert, Stroebe, and van Gieson stains, and we have been able to convince ourselves that the neuroblasts demonstrated by the Golgi method are identical with the proliferated neurilemma cells.

The earliest stage in the formation of a new axis-cylinder when stained by the Stroebe method, is seen to consist in the deposition, along one side of a spindle-shaped neurilemma cell, of a thin thread which grows in length until it projects beyond the limits of the parent cell and stretches on towards its next neighbour in the same longitudinal row. Thus within each old neurilemma sheath numerous new fibres are laid down in short lengths ; these afterwards blend and become continuous so as to form the regenerated axon, which shows evidence of its youth by its greater sinuosity and by the existence of beaded thickenings on it at intervals. As the new axis-cylinders grow in diameter the beadings become gradually less and less evident, until the adult cylindriform axis-cylinder is at length attained.

The new medullary sheath as stained by the Weigert method does not make its appearance until the fourth week, when it too is laid down by a process of secretion along one side of a spindle-shaped neurilemma cell, the medullary sheath being probably wrapped round a pre-formed young axis-cylinder. Like the axis-cylinder, it grows in length until neighbouring myelin sheaths anastomose and form a new and beaded medullary sheath, which progressively grows in thickness and finally loses its beaded appearance.

The observations of Galeotti and Levi (8) are of such interest that we may briefly refer to them at this point. These Italian observers studied the process of regeneration in lizards whose tails had been cut off and in which (in sunny weather) new tails grew

in about fourteen days. In the central stump the nerve fibres degenerated upwards for only a short distance. Regeneration then commenced, the first stage in the process consisting in a proliferation of the neurilemma nuclei, which, as shown in the accompanying drawing, become elongated and arranged in definite rows (Fig. 1). The nucleus of each cell then migrates to one side (Fig. 2). The ends of adjacent cells overlap and fuse together. The new neurilemma sheath is formed at one side of the cell on the side next to the nucleus, while the axis-cylinder appears in the thickest part of the cytoplasm forming, at first, spindle-shaped threads (Fig. 3), which, later, fuse together and make a continuous axon (Fig. 4). The myelin, according to these observers, is formed from the outer part of the cytoplasm. This process in the growing tail of the lizard therefore bears a very striking resemblance to the results obtained in our own series of observations.

(*c*) *Regenerative process in the distal segment of a divided nerve in which the distal segment has not been united to the proximal by sutures.*

The occurrence or otherwise of regeneration in the non-united distal segment of a completely divided nerve forms a crucial

test between the "central" and "peripheral" theories of nerve-regeneration. If new axis-cylinders can only be formed by a process of outgrowth from the central axons, regeneration in the distal segment is obviously impossible under the conditions stated.

But our observations show conclusively that regeneration does occur in the non-united distal segment of a divided nerve-trunk and that the process, as would be expected, is essentially the same as that which occurs in a distal segment which has been joined to the proximal by sutures. The new fibres, however, are somewhat slower in their time of appearing.

New axis-cylinders and medullary sheaths have appeared (in the cat) at the end of four weeks, scantily, and somewhat more profusely at five weeks, after which date they rapidly increase in size. But they never attain to full maturity; they remain permanently in the incomplete beaded stage, unless the distal segment is subsequently joined by sutures to the proximal, when they soon grow to normal dimensions. Evidently some stimulus afforded by the conduction of impulses is necessary in order to permit of their full development.

CONDUCT AND FATE OF TRANSPLANTED NERVE

In certain of our observations, both in the lower animals and in the human subject (see Observations 23, 26, 28, 34, 60, 73, 76, 81, 101, 111, 126, 131, 132, 133), when the gap between the proximal and the distal segment was too great to permit of the two being drawn together by means of sutures, a portion of fresh nerve-trunk was inserted so as to bridge across the intervening gap.

Such a transplanted portion of nerve undergoes degeneration. Leucocytes and connective-tissue cells invade it from without, and

produce fragmentation of its medullary sheaths and axis-cylinders. Regeneration occurs later, but when it does occur it is not from the activity of the cells of the graft itself. Young blood-vessels grow into the degenerated graft, both from the proximal and from the distal segment. Alongside those blood-vessels there are numerous invading neurilemma cells which proceed to lay down new axis-cylinders and medullary sheaths in the usual fashion. New fibres are therefore laid down earliest and most abundantly in the immediate neighbourhood of the invading blood-vessels (see Plate 3, fig. 11). The part of the graft in which new fibres are formed last of all is the central portion, midway between the proximal and distal segments, where the new blood-vessels and invading neurilemma cells are latest in arriving.

The graft, then, acts as a scaffold in which neuroblasts, migrating thither from without, secrete new axis-cylinders and medullary sheaths. Meanwhile the original structure of the graft is entirely absorbed by proliferated connective-tissue cells. Into this new tissue the neurilemma cells, accompanying the blood-vessels, grow and form themselves into longitudinal ribbons or chains as already described.

CLINICAL CONSIDERATIONS

The objects of this research being mainly histological, and our observations having been chiefly made upon the lower animals, the number of clinical observations we have here recorded is not large.

As regards primary suture in dogs, we observed that when the nerve was reunited by sutures immediately after the operative division, motor power first began to reappear in the paralysed

muscles after an interval usually of about four weeks. This date, it will be observed, corresponds to that determined by us as necessary for the process of regeneration to occur. The return of sensation was not recorded in our animals, owing to the difficulty of assuring ourselves of the trustworthiness of such observations.

In one of our cases of transplantation of two inches of sheep's sciatic nerve into a gap in the ulnar nerve in the human subject (Observation 36B) sensation began to return twenty days after the operation, and was perfect six months later.

It has long been known that the function of a nerve-trunk may, in certain cases, be restored if its cut ends be brought together, either immediately after the injury (primary suture) or after an interval of time has elapsed (secondary suture).

In cases of *primary suture*, most surgical observers (Bowlby (3), Thorburn (34), and others) are agreed that restoration of function does not occur, as a rule, until two months after the primary suturing. The earliest possible date in the cat (according to our own observations), by which well-marked regeneration occurs, is four weeks.

A large number of cases of *secondary suture* of nerves have been recorded, in which recovery has occurred. Sensation always returns before motor power in the affected nerve. Thus, so long ago as 1871, Jessop's (15) case of ulnar paralysis of nine years' duration is stated to have shown some return of sensation on the eighth day. In Langenbeck's (20) case of ulnar paralysis of two and a half years' duration, sensation is reported to have returned on the third day, and in Ogston's (24) case of ulnar paralysis, sensation began to return in a week. In one of MacCormac's (21)

cases, after six years' total ulnar paralysis, some return of sensation was reported on the day after operation. In another of his cases, that of ulnar paralysis of six weeks' duration, the result of a bullet wound, the lacerated part of the nerve was excised and the ends joined by sutures : sensation began to return thirteen hours after operation. An unpublished case, observed by ourselves, of an officer who had paralysis of the external popliteal nerve, the result of a bullet wound, showed distinct return of sensation when examined one and a half hours after operation. In Kennedy's (16) four cases sensation commenced to reappear on the third or fourth day after operation, the nerve having been previously paralysed for periods varying between three and eighteen months. Toussaint's (36) case of ulnar paralysis of two years' duration showed some return, both of motion and of sensation, on the third day after secondary suture. Without proposing to enter exhaustively into the literature of secondary nerve suture, we may merely refer to similar cases published by Bowlby (3), de Santi (30), Petrides (26), and Lambotte and Sano (19). Such cases of early return of sensation are readily explained when we remember the mode of regeneration in the distal segment, not by a process of downgrowth from the proximal segment but as a pre-existent accomplished fact—immature, it is true—in the distal segment before reunion had been brought about. Secondary suture in those cases permits of restoration of conductivity in the new fibres already existent in the distal segment by joining them to those of the central segment.

Transplantation of nerve-tissue to bridge across the gap between the proximal and distal segments has yielded widely varying clinical results. Amongst others, we may refer to Damar Harrison's (10) case of median paralysis, in which two inches of

kitten's sciatic were implanted, and where sensation began to improve two days after the operation. Gersung (quoted by Harrison) removed a neuroma from the median nerve and engrafted six centimetres of rabbit's sciatic : sensation began to return in two months. In Mayo Robson's (29) case of median and ulnar paralysis from a scythe wound, two inches of rabbit's spinal cord were implanted in the median gap, whilst the ulnar nerve was united by secondary suture : sensation began to appear in the median area eight days later, whereas the ulnar nerve recovered much more slowly. Peterson (25) transplanted four centimetres of dog's sciatic into both median and ulnar nerves, after an old-standing injury. Sensation began to return on the day after operation, but varied from day to day, increasing more rapidly after the eighth day. Fourteen months later sensation had almost entirely recovered, though motor power had but slightly improved. Peterson himself, whilst holding that regeneration occurs by a downgrowth of axis-cylinders from the central segment, admits that sensation returns before there has been time for such downgrowth to occur and attempts to explain this by the theory of "transmission of sensation through other tracts, the inhibitory influence of the irritated central nerve-ends having been removed by the operation."

All these results are very contradictory. In one of our own cases of ulnar paralysis, where two inches of sheep's nerve had been transplanted, some return of sensation was first observed on the twentieth day. In another case of sciatic paralysis, where six inches of bullock's sciatic had been transplanted, no return of sensation had occurred up to the time of writing, five months after the operation.

CHAPTER VII

THE NEURONE THEORY

The occurrence of regeneration in peripheral nerves, not by a downgrowth from the axis-cylinders of the central segment but by a process of secretion by proliferated neurilemma cells or neuroblasts in the distal segment itself, has obviously a most important bearing upon our conception of the histogenetic structure of the peripheral nervous system, and upon the doctrine—at present a widely popular one—of the Neurone Theory.

The essential idea of Waldeyer's neurone theory, in his own words (38), is that "das Centralorgan ein Conglomerat unzähliger Nervencellenindividuen ist, dass also alle Nervenfasern nichts anderes sind als Zelleibsbestandtheile je eines bestimmten Nervencellenindividuums, und dass die graue Substanz auch nichts anderes ist als der Ausdruck einer Maasenansammlung von Nervencelleibsbestandtheilen, und zwar je eines bestimmten Nervencellenindividuums." This concept of the nervous system as consisting of innumerable anatomically independent nervous units or neurones, in contiguity but not in continuity with each other, based as it was upon Ramón y Cajal's results with the Golgi impregnation method, offered a most attractive scheme, which not only apparently

afforded a clear plan of the structure of the nervous system, but also seemed to be in close agreement with pathological results, more especially as regards degenerations.

Amongst the statements supporting the neurone theory, the most important have been the following :—

(1) The embryological results of His and others, according to which each axon, whether of the central or of the peripheral nervous system, is a mere outgrowth or process of a nerve cell.

(2) The appearance demonstrated by Cajal, Lenhossek, and others by the Golgi and methylene-blue methods, according to which the different "neurones" appear to be anatomically independent of each other.

(3) The occurrence of degeneration in an axis-cylinder if it be cut off from its parent cell, such degeneration being strictly limited to the particular neurone involved and not extending to adjacent neurones.

(4) The regeneration of peripheral nerves, after their division, by a process of downgrowth from the axons of the central segment (Huber, Stroebe, Vanlair, etc.).

Whilst we do not attempt to deal exhaustively here with all the arguments raised in such a discussion, we would remark that the above views are by no means unassailable. Thus it has been urged by Held, Dogiel, Bethe and others that the silver method gives "neurone pictures" only in embryos or in young animals in which development is not complete ; that in fully-grown animals there exists a concrescence or anastomosis between processes from different nerve-cells, and that the end-knobs which cap the terminal arborisations are really artefacts, due to essential imperfections of the Golgi and methylene-blue methods, the appearance, as Hill (12)

states, being obtained by methods which colour merely the cytoplasm, and leave the conducting elements uncoloured.

That degeneration is not necessarily confined to the limits corresponding to one of Waldeyer's neurones has recently been pointed out by Nissl (22). One of us (32) has also recorded the fact that ascending degeneration of the posterior columns of the cord does not always stop short at the gracile and cuneate nuclei as is commonly stated, but moves onwards beyond these nuclei into the arcuate fibres of the medulla.

Finally, according to the neurone theory, regeneration ought to be impossible in a peripheral nerve-trunk whose connection with its trophic centres (in the anterior cornu or posterior spinal-root ganglion) has been severed. Our results however, show that the true source of the regenerative process in peripheral nerves is to be sought, not in the cells of the anterior cornu or posterior root ganglion, but in the neurilemma cells of the nerve-trunk itself.

Upon the question of the embryonic origin of the neurilemma cells, whether epiblastic or mesoblastic, we do not feel warranted in expressing an opinion. But it is evident that the peripheral nervous system is to be regarded as composed of chains of neuroblasts (from whatever embryonic layer derived) fused together to form continuous axons enclosed within medullary and neurilemma sheaths.

The correctness of this view is emphasised when we recall the fact that structural regeneration of axis-cylinders has not been observed in the central nervous system. Thus, even under the most favourable conditions, as, for example, in cases of experimental hemisection of the cord, when the fibres of the various tracts have simply been divided and the cut ends left in close apposition,

no regeneration occurs—simply degeneration followed by sclerosis; and yet no such obstruction exists between the cut ends as in the case of a divided peripheral nerve-trunk where regeneration does occur. The explanation of this, we would submit, is to be associated with the presence of neurilemma cells in the peripheral nervous system in their absence from the cerebro-spinal axis. In certain cases of experimental section of the cord, it is true, young fibres have been observed scantily distributed at the periphery of the cord (Schmaus-Sacki, *Pathologische Anatomie des Rückenmarks*, 1901, p. 378), but these new fibres possess a nucleated neurilemma sheath and are therefore obviously of the "peripheral" type. They are, moreover, apparently continuous with the neurilemma-clothed fibres of the nerve roots, anterior or posterior, and are most abundant along the course of newly-formed blood-vessels.

The presence of a neurilemma sheath constitutes no mere minor difference between the nerve-fibres of the central and those of the peripheral nervous system. It is of fundamental significance, since upon the presence of neurilemma cells depends the possibility of regeneration and recovery after injury.

The neurone theory, in so far at least as it applies to the peripheral nervous system, must in our opinion be discarded. The peripheral nervous system is to be considered as made up of chains of cells, set end to end, whose axis-cylinder processes fuse together to form continuous paths—the peripheral axis-cylinders.

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